Signal transduction pathway activation in RAW 264.7 murine macrophages exposed to *Eurotium amstelodami* purified toxins and β (1, 3) D-glucan

by

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**Abstract**

Mold growth in buildings is known to be associated with both allergenic and non-allergenic effects on population health. The mechanisms by which this process occurs, however, are not well understood. The objectives of this study are as follows: 1) Identify which transduction pathways are activated in RAW 264.7 cells following mycotoxin and glucan exposure, 2) Determine if there is time- and/or dose- dependency, and 3) Identify any interactions between mycotoxin and glucan. Molecular techniques will be implemented to accomplish these objectives. Results have identified which transduction pathways are activated following mycotoxin and glucan exposure. Generally, these pathways are up-regulated at 1h post exposure (PE) to Neoechinulin A and B. However, for glucan exposed AMs, the trend seems to be down-regulation after 30m and 1h PE and up-regulation after 2h PE. Additionally, this study provides support for both synergistic and antagonistic interactions between Neoechinulin A and glucan.

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**Figure 15.** Gene expression changes in AMs after simultaneous exposure to Neoechinulin A and β (1, 3) D-glucan simultaneously at concentrations of $10^{-10}$M for 30m, 1h and 2h exposures compared to Neoechinulin A and β (1, 3) D-glucan alone.

Chapter 1

1.1 General Introduction

1.2 Introduction to Fungi

Fungi are common in both outdoor and indoor environments. In outdoor air, mold exposure has been linked to respiratory health problems as far back as 400 BC and continues to be recognized to date (Dales *et al.*, 1991; Brunekreef *et al.*, 1992; Spengler *et al.*, 1994; Garrett *et al.*, 1998; Lander *et al.*, 2001; Pinto *et al.*, 2002). Exposure to fungi in outdoor environments has been linked to asthma and allergy. In North America alone, about 10% of the population is allergic to *Cladosporium,* the most commonly encountered fungal genus in outdoor air, and dominated by *C. cladosporioides* and *C. herbarum*. Asthma onset caused by fungal exposures also represents 8% of all hospital emergency admissions (NAS, 2000).

Fungi are also found in indoor air. In healthy, dry buildings, the species composition of fungi found indoors is similar to that encountered outdoors. However, in damp buildings the composition of fungal species is distinctly different from that encountered outdoors. In 15-20% of buildings surveyed in Atlantic Canada some degree of water damage, which contributes to fungal growth has been reported (Rand, 1999). Additional research has shown that 20-25% of homes in Atlantic Canada have dampness problems, which contributes to mold growth. Other areas of Canada and Northern temperate areas have also shown comparable results (Murtoniemi, 2003). This is an important finding as Canadians have been shown to spend almost 90% of their time indoors (Leech *et al.*, 1997).

In damp buildings, many of the same fungi species that are found outdoors are recovered indoors as well, for example, *Cladosporium* spp. (Rand, 1999). However, the most commonly encountered fungi inside damp buildings are anamorphic, soil-dwelling Ascomycetes such as *Aspergillus* spp., *Penicillium* spp. such as *P. aurantiogriseum, P. brevicompactum, P. chrysogenum, P. crustosum, P. viridicatum,* and a variety of other species such as *Eurotium herbarorium, Eurotium amstelodami Paecilomyces variotii, and Stachybotrys chartarum* (Rand, 2005; Slack *et al.*, 2009), which are mostly toxigenic. Indoor inhalation exposure to these types of fungi is recognized as a contributing factor to many health problems, including childhood asthma and allergy. However, effects associated with indoor fungi differ from those associated with allergy and asthma (NAS, 2004). These effects have been related to lower respiratory symptoms such as hemoptosis and pulmonary hemosiderosis (Dearborn *et al.*, 1999) in environments where individuals are exposed to high spore loads. However, other symptoms have been reported; wheeze, cough and headaches (Dales *et al.*, 1991). It is thought that the variety of symptoms are linked to exposure to not only fungi that are allergenic but also toxigenic.

The majority of fungal spores are found in settled dust (Ferro *et al.*, 2004). Microscopy has revealed that dust contains a mixture of organic particles such as pollen, plant material, fungal spores, textile fibers, skin cells, arthropod pieces, insulation fibers, and carpet backing and inorganic material such as silica (Rand, 2007). Fungal composition in dust can comprise up to $10^6$ to $10^7$ spores/g wt of dust in damp buildings (Rand, 2007). Surprisingly, over 60 % of this fungal material in dust is respirable. Ultra fine fungal fragments are within the range of 2.5 um and less than 1.0um. In humans,

respirable particles are defined as anything equal to or smaller than 5.0 μm in diameter. There are few quantitative data on the amount of toxins in spores. However, it has been reported that the concentrations of mycotoxins in spores and spore fragments are in the range of $10^{-4} - 10^{-5}$M (Wicklow and Shotwell, 1983; Sorenson et al., 1987; Miller, 1992).

1.3 *Eurotium amstelodami* and neoechinulins

*Eurotium amstelodami* is a soil dwelling, xerophilic (dry loving) species that is most frequently recovered from tropical and subtropical regions worldwide. In these regions, the species is most frequently reported from cultivated soil and a high number of isolates have been reported from stored and/or decaying grains, nuts and dried fruit samples. Is is not known to be pathogenic, although isolates have been recovered from the digestive tract of the honey bee (*Apis mellifica)*. Physiological, developmental and cultural characteristics of this species have been the subject of a review by Domsch *et al.* (1993) and for additional information; the reader is referred to this reference. In North America, *Eurotium amstelodami* is commonly found on mold damaged, gypsum wallboard, manufactured wood, ceiling tiles, insulation, and textiles that have been damp or subject to periodic condensation (Flannigan and Miller, 2001; Miller *et al.*, 2008). *Eurotium amstelodami* is also known to produce mycotoxins. Neoechinulin A & B and epiheveadride have been identified as major secondary metabolites of this filamentous fungus (Slack *et al.*, 2009).

1.4 Immune responses to fungi

Animal studies have clearly shown that exposure to these toxic spores stimulate inflammatory lung responses, exhibited as molecular, biochemical, micro-anatomical, anatomical and pathophysiological changes (Nikulin *et al.*, 1997; Rao *et al.*, 2000, 2004;

Flemming, 2003; Miller *et al.*, 2003; Rand *et al.*, 2005; Rand *et al.*, 2006). Present in the fungal spore wall are compounds called mycotoxins. Additional experiments have been conducted with purified toxins to determine its effects on the inflammation process. In a study conducted by Vanderbilt *et al.* (2003), freshly isolated alveolar type II cells (ATIIs) were found to express certain chemokines, especially the CXC family of proinflammatory chemokines following lung injury. Additionally, it was found that ATIIs as well as interstitial fibroblasts were highly sensitive to pure mycotoxins isolated from *Penicillium chrysogenum* and *Stachybotrys chartarum* showing differential up-regulated surfactant protein and inflammatory gene expression at toxin concentrations in the low nM range (Robbins, 2007). Robbins (2007) also showed distinct gene expression differences in ATIIs exposed to both atranones A and C. This was a very interesting finding as these two mycotoxins differ only by the presence/absence of a double bond at C12. This type of differential response was also reported by Rand et al. (2006) who exposed mice to both atranones A and C resulting in significant differential protein expression patterns in the bronchioalveolar lavage fluid (BALF). A similar study that exposed primary alveolar macrophages (AMs) to pure toxins isolated from *Eurotium amstelodami, Eurotium herbariorum Aspergillus versicolor* and *Penicillium brevicompactum* also showed differential up- and down- regulation of inflammatory genes, which was both toxin and time- dependent (DiPenta, 2008). Another interesting finding of the DiPenta (2008) study was differential gene expression patterns in AMs following exposure to neoechinulin A and B. These two mycotoxins also differ only by the presence/absence of a double bond at C14. Both *in vitro* and *in vivo* studies have shown that exposure to either pure or spore sequestered mycotoxins leads to depressed

alveolar macrophage (AM) activity and an increased inflammatory response (Sorenson *et al.*, 1987; Plascencia and Rosenstein, 1990; Routsalainen *et al.*, 1998).

With respect to signal transduction pathway activation after immune responses, some researchers have predicted that the cell responses to mycotoxins will follow the cell-stress activated p38 and/or Jun N-terminal Kinase (JNK) pathways (Raingeaud *et al.*, 1995; Yang *et al.*, 2000). When AMs were exposed to *Stachybotrys chartarum* purified toxins (trichothecenes) the mitogen-activated protein kinase (MAPK) pathway was activated via the mechanism known as the ribotoxic stress response (Pestka *et al.*, 2004). Wang and Yadav (2007) hypothesized that the *Stachybotrys chartarum* toxins induce multiple signaling pathways in AMs, including MAPK pathways and death receptor mediated pathways, and other cross-talk pathways. From these studies, it is clear that mycotoxins induce multiple signaling pathways, and that there is evidence suggesting there is cross-talk between the pathways.

Interactions between mycotoxins, fungal and bacterial spores on cell immune responses have been studied. Studies show synergistic, antagonistic and additive toxicity effects after simultaneous exposures. One study has shown that combinations of *Stachybotrys chartarum* spores with the spores of *Streptomyces californicus* had a clear synergistic effect on the production of an inflammatory mediator (cytokine) in mouse macrophages (Huttunen et al., 2004). Another study showed that after exposure to the spores of co-cultivated *S. californicus* and *S. chartarum* there was a significant influence on the regulation of cell cycle arrest compared to either spore alone (Pettinen et al., 2005). Other studies examining mixtures of mycotoxins also found combination effects that were stronger than one mycotoxin alone (Thuvander et al., 1999; Tammer et al.,

2007). Tammer et al. (2007) applied an established model for immunotoxic studies using stimulated human peripheral blood mononuclear cells (PBMC) and showed that the effects on cytokine production of mixtures of mycotoxins was stronger than the effects caused by the toxins applied singly. A different study, however, showed no synergistic effects, but rather, additive toxicity and antagonistic effects (Thuvander et al., 1999). Human lymphocytes were exposed to a combination of nivalenol and T-2 toxin which resulted in additive toxicity. Interestingly, when T-2 toxin was combined with deoxynivalenol the result was an inhibition of the proliferative response that was significantly lower than the individual toxins which showed an antagonistic action.

1.5 β-glucans and Dectin-1

Fungal spore walls, in addition to containing allergens and toxins, are also composed of sugars such as beta (β)-glucans. β-Glucans are found in higher plants, some bacteria, algae, and fungi (Reid *et al.*, 2004; Dalmo & Bøgwalg, 2008; Harada & Ohno, 2008). β-glucans are a major constituent of the fungal spore cell wall to which they provide mechanical strength (Stone and Clarke 1992) via their glucose polymer backbone of β (1, 3) linked β-D-glucopyranosyl units with β (1, 6) linked side chains of various arrangements (Shematek *et al.*, 1980; Duffus *et al.*, 1982; Williams *et al.*, 1997; Ormstad *et al.*, 2000; Harada & Ohno, 2008). β (1, 3) glucans are considered to be potent inflammatory mediators due to their linear structure (Young *et al.*, 1998).

Levels of β (1, 3) D-glucan have been reported in building environments in Sweden and can range from 0.1 ng/m$^3$ in office buildings to 106 ng/m$^3$ in houses in which mold was evident (Rylander *et al.*, 1992; Rylander *et al.*, 1994). In a separate study, an average level of 15.3 ng/m$^3$ of β (1, 3) glucan was recorded in schools that had

reports of mold damage, compared to only 2.9 ng/m$^3$ of β (1, 3) glucan recorded in control schools (Rylander *et al.*, 1998). It is important to note that these ranges could apply to other regions that have a similar climate as Sweden (Ormstad *et al.,* 2000). In urban homes in Ottawa, Miller *et al.* (2007) reported levels of 1.30 to 1.46 ng/m$^3$ throughout various parts of the home. The concentrations of β (1, 3) glucan were found to vary from area to area. It is highly dependent on environmental factors in the area as well as which fungal species are present.

Most research performed on the pulmonary effects of β (1, 3) glucans has been conducted using zymosan and curdlan as models. Zymosan is a glucan derived from yeast and is a mixture composed of linear β (1, 3) glucan and a more complex β (1, 6) glucan (both present in a 1:1 ratio), mannan, proteins, chitin, and glycolipids (Brown *et al.,* 2002; Kataoka *et al.*, 2002; Dalmo & Bøgwalg, 2008). Curdlan is a pure linear type of β (1, 3) glucan produced by bacterial species belonging to the genera *Alcaligenes* and *Agrobacterium* (Lee, 2005). In a study by Kataoka *et al.* (2002), various β glucans were screened for their potential to activate the NF-kB pathway in RAW 264.7 cells. The glucans screened by this study included both linear and branched forms of β (1, 3) glucan. The results obtained from this study indicate that the linear β (1, 3) glucan curdlan exhibits significant cell-stimulating activities, and that the activities of β (1, 3) glucans are dependent on their lengths and conformations.

*In vitro* studies, using AMs have shown that cells exposed to β glucan produce various inflammatory cytokines, in particular TNF (Adachi *et al.*, 1997). Young *et al.* (2001) showed that intratracheal instillation of β (1, 3) glucan (zymosan A) induced pulmonary inflammation in rats. They observed a variety of pulmonary changes such as

increases in respiration, and infiltration of polymorphonucleocytes into the airspace, both of which were dose-dependent. An *in vivo* study by Fogelmark *et al.* (1997) showed that guinea pigs exposed to β (1, 3) glucan had increased numbers of eosinophils in their airways. Interestingly, the eosinophil numbers found after β (1, 3) glucan exposure were decreased by simultaneous exposure to endotoxin (LPS). This finding suggests that endotoxin and β (1, 3) glucan activate different inflammatory mechanisms when inhaled.

Dectin-1 has been identified as the major β (1, 3) glucan receptor and is a small, type II transmembrane receptor (Brown and Gordon, 2001) and is classed as a type-C lectin, with a carbohydrate recognition domain, a short stalk, and a cytoplasmic tail possessing an immunoreceptor tyrosine-base motif (Weis *et al.*, 1998; Ariizumi *et al.*, 2000; Brown and Gordon, 2001). In humans, dectin-1 is approximately 70% identical to the mouse receptor at the amino acid level and both have similar structures and responses (Willment *et al.*, 2001). This receptor has been shown to recognize the β-glucans in zymosan, *Saccharomyces cerevisiae,* and heat-killed *Candida albicans* (Brown and Gordon, 2001). Dectin-1 expression on macrophages, neutrophils, monocytes and dendritic cells has been demonstrated (Brown *et al.,* 2002; Brown *et al.,* 2003; Willment *et al.,* 2003). Dectin-1 has an association with toll-like receptor 2 (TRL2) for initiating the immune response in alveolar type II cells exposed to zymosan. Dectin-1 is responsible for the reception of β-glucan while the TLR2 binds to an indistinct component of the yeast cell wall (Gantner *et al.*, 2003; Willment *et al.,* 2003).

## 1.6 Model System

Alveolar macrophages (AMs) are vital to lung immune responses against both infectious agents such as bacteria and certain fungi and also to non-infectious substances such as mycotoxins (Liu *et al.*, 2002). AMs have been found to play a crucial role in phagocytosis of foreign particles, production of mediators of cellular immunity, and regulation of T-lymphocyte activity (Gerberick *et al.*, 1984; Rossi *et al.*, 1986). Gregory *et al.* (2004) showed that alveolar macrophages respond to mycotoxins. Using immunochemistry techniques, localization of satratoxin H was shown in walls of *S. chartarum* spores, its diffusion into inflamed mouse lung tissue surrounding spores, and incorporation of the mycotoxin into AM lysosomes. Later studies revealed AM recruitment in lungs of animals exposed to *S. chartarum* spores (Yike *et al.*, 2007). Both *in vitro* and *in vivo* studies have shown that exposure to either pure or spore sequestered mycotoxins leads to depressed AM activity and an increased inflammatory response (Sorenson *et al.*, 1987; Plasencia and Rosenstein, 1990). Other studies showed that fungal metabolites or toxins may also affect the function of AMs (Sakurai *et al.*, 1997; Ortiz *et al.*, 1998). Therefore, changes of any of the molecular features leading to biochemical changes of AMs due to toxin exposure could lead to pulmonary and/or systemic damage (Jakab *et al.*, 1994).

## 1.7 Overall Purpose

The overall purpose of this study is to provide insight into the molecular mechanisms inducing inflammatory responses in AMs. The objectives of this study are as follows: 1) Identify which transduction pathways are activated in RAW 264.7 murine macrophages (AMs) following mycotoxin and glucan exposure, 2) determine if there is

time- and/or dose- dependency, and 3) identify any interactions between mycotoxin and glucan. Chapter 2 deals with which transduction pathways are activated in AMs upon mycotoxin and glucan exposure, any dose- and/or time-dependent patterns with this activation, and cytotoxicity of the compounds tested. Chapter 3 focuses on the outcome of any interactions between mycotoxins and glucans.

It is hypothesized that neoechinulin A, B and β (1, 3) D-glucan will activate signal transduction pathways in AMs; that this activation will show differential patterns of expression; that it will show time and dose-dependency; and that simultaneous exposure to both neoechinulin A and β (1, 3) D-glucan will elicit a synergistic response.

Chapter 2– Dose and time dependent responses in AM signal transduction pathways after exposure to neoechinulins A & B and β (1, 3) D-glucan.

## 2.1 Introduction

Mold growth in building environments is associated with both allergenic and non-allergenic effects on population health (NAS, 2004; Health Canada, 2004; WHO, 2004). Species found growing indoors comprise a small but dominant proportion of fungi that produce mycotoxins (Nielsen *et al.*, 1998; Jarvis, 2002; Nieminen *et al.*, 2002). Most species of fungi that are found indoors produce spores that contain relatively high concentrations of mycotoxins, but also contain species-specific allergens and proteases bound by a cell wall made of β (1, 3) D-glucan (Rand, 2007).

*Eurotium amstelodami* is commonly found in indoor environments that suffer from water damage (Flannigan and Miller, 2001; Miller *et al.*, 2008). Neoechinulin A &

B have been identified as major secondary metabolites of this filamentous fungus (Slack *et al.*, 2009).

The major route of human exposure in indoor environments is by the inhalation of toxin-containing spores or free, toxin-contaminated, dust particles (Brasel *et al.*, 2005). These inhaled particulates are subjected to phagocytosis and clearance by the host alveolar macrophages (AMs) These AMs act as a crucial first line of innate defense in the host lung against inhaled particulates (Dorger and Krombach, 2002). For this reason, it is important to understand the mechanisms underlying the toxicity of mycotoxins towards AMs.

Eukaryotic cells respond to both intracellular and extracellular stimuli via signal transduction pathways. These comprise molecular and biochemical cascades, which in turn produce unique responses in the cells. These pathways should not be considered mutually exclusive, cross-talk is likely to occur in order to fine tune a cell response to a given stimulus. Signal transduction pathways for the immune response have been studied and some researchers have predicted that the immune response to mycotoxins will follow the cell-stress activated p38 and/or Jun N-terminal Kinase (JNK) pathways (Raingeaud *et al.*, 1995). Other researchers have found that AMs exposed to *Stachybotrys chartarum* purified toxins (trichothecenes) activate the mitogen-activated protein kinase (MAPK) pathway via the mechanism known as the ribotoxic stress response (Pestka *et al.*, 2004). Wang and Yadav (2007) hypothesized that the *Stachybotrys chartarum* toxins induce multiple signaling pathways in AMs, including MAPK pathways, death receptor mediated pathways, and related cross-talk. Pathway studies agree that mycotoxins induce

multiple signaling pathways, and that there is evidence of cross-talk between the pathways.

The purpose of this study is to determine which transduction pathways are stimulated in RAW 264.7 cells following exposure to neoechinulin A & B and β (1, 3) D-glucan. To determine if there are any dose- and/or time-dependent patterns of expression, to determine any cytotoxic properties of these compounds, and also, to determine the no observed adverse effect level (NOAEL) for exposure. Based on previous studies involving cytokine expression in AMs exposed to neoechinulins and β (1, 3) D-glucan (Dipenta, 2008), it is hypothesized that activation of signal transduction pathways will be a time- and dose-dependent reaction.

## 2.2 Materials and Methods

### 2.2.1 Toxins

Neoechinulin A & B (Fig 1-2) from *Eurotium amstelodami* were isolated, purified and identified, by Dr. David Miller, Department of Chemistry, Carleton University, Ottawa.

Each toxin was dissolved in 1 mL of 100% EtOH and then diluted in 100 mL of 10% EtOH , endotoxin free saline (PBS) to a concentration of $10^{-5}$ M. The solutions were diluted into a working solution of $10^{-7}$M. β (1, 3) D-glucan (curdlan from *Alcaligenes faecalis* (Sigma Aldrich C7821, lot # 89H4032 ≥ 99% purity (from J.D. Miller), which was chemically characterized by Foto et al. (2005)) was used as a positive control. β (1, 3) D-glucan was dissolved in 1 mL of 0.3 M sodium hydroxide and then diluted in 100 mL PBS to a concentration of $10^{-5}$ M. Both toxins and β (1, 3) D-glucan were

administered to the cell culture in single doses at concentrations of $10^{-8}$, $10^{-9}$, $10^{-10}$, $10^{-11}$ and $10^{-12}$M.

### 2.2.2 Cell Culture

The RAW 264.7 murine macrophage cell line was obtained from the American Type Culture Collection (Rockwille, MD, USA). Cells were maintained at 37°C in a 5% $CO_2$ humidified incubator in RPMI 1640 (Invitrogen) medium supplemented with 10% (v/v) heat inactivated fetal bovine serum (FBS, Invitrogen) and 100 U/ml penicillin and 100 μg/ml streptomycin (Sigma). Macrophage cell numbers were assessed using a hemacytometer.

### 2.2.3 Experimental Design

RAW 264.7 murine macrophages were exposed to neoechinulin A & B for 30m, 1h and 2h at $10^{-8}$, $10^{-9}$, $10^{-10}$, $10^{-11}$ and $10^{-12}$M concentrations. Both positive and diluent controls were used. β(1,3) D glucan was used as a positive control while the diluents for each toxin was used as a diluent control. All experiments were performed in triplicate.

At the end of the desired exposure time, the reactions were stopped by draining the medium and rinsing the flasks with 2ml sterile PBS. Following rinsing, 1.25ml RNAlater® was added to each flask, cells were scraped into 2ml eppendorf tubes and stored at -80◦C.

### 2.2.4 Cell Viability

AMs were seeded at 30,000 cells/well of a 96-well plate and allowed to adhere and grow for 48h. The cells were exposed to neoechinulin A & B, β(1,3) D glucan at concentrations ranging from $10^{-8}$ to $10^{-12}$M and diluent controls for 2h. Following this, 10 ul MTT reagent was added to the culture medium in the wells of the 96-well plate, and incubated for 3h at 37°C. Media was then removed and replaced with 100 ul acidified detergent reagent (4 mM HCl, 10% Triton-X in isopropanol). The plate was shaken in the dark at room temperature for 15 mins and the absorbance was measured at 570 nm. The MTT assay measures the ability of the cells to transform MTT to formazan that can be spectrophotometrically detected at a wavelength of 570 nm with a microplate reader. Cell viability was calculated as percentage by comparing absorbance values from cells exposed to toxins compared with those from corresponding control cells.

### 2.2.5 RNA Extraction

Total RNA isolation was performed using RNeasy® mini kit (Qiagen), according to the manufacturer's specifications. Briefly, treatment and control cells were disrupted using Buffer RLT (Qiagen) and homogenized using a sterile syringe and needle. Lysate was precipitated using 70% EtOH followed by centrifugation (10,000 rpm for 15 sec) in an RNeasy column to collect RNA. The column containing RNA was washed in RWI buffer (Qiagen), treated with RNase-free DNase to eliminate DNA contamination according to manufacturer's instructions (Qiagen), and then washed again with RWI followed by two washes with RPE buffer (Qiagen). After washing, RNA was resuspended in RNAse/ DNase free water (Sigma Aldrich). The concentration of RNA in

samples was determined using a NanoDrop® ND-1000. RNA integrity and purity was assessed 260/280 nm and 260/230 nm ratios. Samples with a 260/280 nm ratio of ≥ 2.0 and a 260/230 nm ratio ≥ 1.90 were used for qPCR analysis.

### 2.2.6 Reverse Transcription PCR

Reverse transcription (RT) Polymerase Chain Reaction (PCR) reactions were carried out using a reaction ready first strand cDNA synthesis kit (C-03 SA Biosciences ®) according to manufacturer's instructions. An annealing mix was prepared first by combining 1 µg of RNA with 2 µL of GE Buffer (5x genomic DNA elimination buffer), the final volume was adjusted to 10 µL with RNase-free water. This annealing mix was preheated at 42°C for 5 minutes then combined with a RT cocktail (4 µL 5x RT buffer (BC3), 1 µL primer and external control mix (P2), 2 µL RT enzyme (RE3), and 3 µL of RNase-free water). The RT reaction was performed as follows; 42°C for 5 minutes, followed by heating at 95°C for 5 minutes to degrade the RNA and inactivate the RE3. All cDNA was stored at -20°C.

### 2.2.7 Real-time PCR

Two types of real-time (q) PCR were used in this study. For the transduction pathway screening experiments mouse signal transduction pathwayfinder™ PCR arrays were used (SA Biosciences # PAMM-014) Following the RT reaction, cDNA samples were diluted with 91 µL of RNase-free water. Next, each cDNA sample was combined with 200 µL of the PCR SYBR green master mix (SA Biosciences) and 110 µL RNase-free water. This solution was added in 25 µL aliquots to each well of a 96-well PCR plate

for mouse signal transduction pathway finder (SA Biosciences ®). The 96-well plates contain primers for specific genes of interest (including housekeeping genes for reference). The array contains specific genes representing 18 signal transduction pathways, 2 housekeeping genes, a mouse genomic DNA contamination control, 3 reverse transcription controls, and 3 positive PCR controls (Table 1). The no reverse transcription control (NRT) was made through a combination of a 1 in 100 dilution of the original RNA in RNase-free water with PCR master mix and RNase-free water. The q PCR reactions were carried out using an ABI Prism 7000 Sequence Detection System® (Applied Biosystems). A two-step cycling program q PCR reaction was performed (Figure 3). The first step was 10 minutes at 95°C to activate the hotstart DNA polymerase, next there were 40 cycles for amplification starting at 95°C for 15 seconds, and then the temperature was lowered to 60°C for 60 seconds in order to detect SYBR green fluorescence.

For the dose and time dependent experiments, customized primers and q PCR protocols were used. From results of the transduction pathway screening, forward and reverse PCR primers for the genes of interest (Table 2) were designed using Primer 3 and custom synthesized by Integrated DNA Technologies. The q PCR protocol (Figure 4) was carried out on an ABI Prism 7000 Sequence Detection System® (Applied Biosystems). A two-step cycling program q PCR reaction was performed. The first step was 10 minutes at 95°C to activate the hotstart DNA polymerase, next there were 40 cycles for amplification starting at 95°C for 15 seconds, and then the temperature was lowered to 55°C for 60 seconds in order to detect SYBR green fluorescence.

For both protocols, relative gene expression was determined according to the comparative $C_t$ method, with the Actb housekeeping gene and diluent control references set as the calibrators. Fold change equals $2^{\Delta\Delta Ct}$, where the $C_t$ is the threshold cycle, $\Delta C_t$ is the difference between the $C_t$ values of the target gene and the internal control gene, $\Delta\Delta C_t$ represents the difference between the $\Delta C_t$ value for the control cells and treated cells.

### 2.2.8 Statistical Analysis

A Shapiro-Wilk test for normality was performed to verify if the samples were normally distributed. Data (n=3) were then tested for statistical significance using two-way analysis of variance (ANOVA). Bonferroni post test was also used to examine differences between control and treatment gene expression data. Statistical analysis was carried out using Graph Pad Prism version 4.0 and results were considered significant at $\alpha \leq 0.05$ (Gotelli and Ellison, 2004). For graphical representation, data were log transformed. For detailed ANOVA tables the reader is referred to appendices I-III, V-VII.

## 2.3 Results

### 2.3.1 Transduction pathway screening experiment

In order to determine which transduction pathways are activated, RAW 264.7 cells were exposed to neoechinulin A & B at $10^{-8}$M concentration for 2h. For the rest of the experiments, only genes that were significantly regulated are assayed. A heat map was generated to assess the degree of gene regulation (Fig 3).

1) Neoechinulin A

After 2h exposure to $10^{-8}$M neoechinulin A, AMs showed significant ($p \leq 0.05$) down-regulation of 5 genes representing 7 out of 18 transduction pathways assayed (Table 3). These significantly down-regulated genes were Bmp2, Hspb1, Icam1, Vegfa and Cdknlb. These genes are indicators for the hedgehog pathway, stress pathway, phospholipase c/NFkB pathways, Wnt pathway, and TGF-B pathway, respectively.

2) Neoechinulin B

After 2h exposure to $10^{-8}$M neoechinlulin B AMs showed significant ($p \leq 0.05$) down-regulation of 2 genes representing 2 out of 18 transduction pathways assayed (Table 3). These genes were Bmp2 and Cd5. These genes represent the hedgehog pathway and the NFAT pathway, respectively.

### 2.3.2 Dose dependant experiments

For dose-dependent experiments, AMs were exposed to either neoechinulin A, neoechinulin B or β (1,3) D glucan at concentrations of $10^{-8}$M, $10^{-9}$M, $10^{-10}$M, $10^{-11}$M, $10^{-12}$M. To evaluate time-dependent trends, these experiments were conducted at 30m, 1h, and 2h time periods.

1) Bmp2

*Neoechinulin A* – Bmp2 was significantly up-regulated at 1h PE for $10^{-8}$M, $10^{-9}$M, $10^{-10}$M and $10^{-11}$M, but not $10^{-12}$M. At 2h PE, it was significantly up-regulated at$10^{-10}$M, $10^{-11}$M and $10^{-12}$M but not at $10^{-8}$M and $10^{-9}$M. It was not significantly changed at 30m PE for any doses tested (Fig 4 a-c).

*Neoechinulin B* – Bmp2 was only found to be significantly up-regulated at 1h PE for $10^{-8}$M. It was not significantly changed at 30m or 2h PE for any doses tested (Fig 4 d-f).

*β (1,3) D glucan* – At 30m PE, Bmp2 was significantly down-regulated at $10^{-9}$M. While at 1h PE, it was significantly down-regulated for $10^{-8}$M and $10^{-9}$M exposures. Bmp2 was not significantly changed at 2h PE for any doses tested (Fig 4 g-i).

2) Hspb1

*Neoechinulin A* – Hspb1 was significantly up-regulated at 1h PE for $10^{-8}$M, $10^{-9}$M, $10^{-10}$M and $10^{-11}$M, but not at $10^{-12}$M. At 2h PE, it was found to be significantly up-regulated at $10^{-10}$M and $10^{-11}$M but not at $10^{-8}$M, $10^{-9}$M and $10^{-12}$M. It was not found to be significantly changed at 30m PE for any doses tested (Fig 5 a-c).

*Neoechinulin B* – At 30m PE, Hspb1 was significantly up-regulated for $10^{-10}$M, $10^{-11}$M and $10^{-12}$M. At 1h PE, it was significantly up-regulated for $10^{-8}$M, $10^{-11}$M and $10^{-12}$M. At 2h PE, Hspb1 was significantly up-regulated for $10^{-9}$M and $10^{-10}$M and $10^{-11}$M only (Fig 5 d-f).

*β (1,3) D glucan* – Hspb1 was found to be significantly changed at 30m PE at $10^{-8}$M only. No changes occurred at other doses tested at 30m, or all doses tested at 1h or 2h PE compared to controls (Fig 5 g-i).

3) Icam1

*Neoechinulin A* – At both 30m, 1h and 2h PE, Icam1 was significantly up-regulated at all concentrations tested (Fig 6 a-c).

*Neoechinulin B* – At 30m and 2h PE, Icam1 was significantly up-regulated at each concentration tested. At 1h PE, it was significantly up-regulated at $10^{-8}$M, $10^{-9}$M, $10^{-11}$M and $10^{-12}$M, but not at $10^{-10}$M (Fig 6 d-f).

*β (1,3) D glucan* – Icam1 was significantly down-regulated at $10^{-8}$M for 1h PE and significantly up-regulated at $10^{-10}$M for 2h PE. It was not significantly changed at 30m PE for any doses tested (Fig 6 g-i).

4) Vegfa

*Neoechinulin A* – Vegfa was significantly up-regulated for every dose tested for 30m, 1h and 2h PE (Fig 7 a-c).

*Neoechinulin B* – At 30m PE, Vegfa was significantly up-regulated for all doses tested. At 1h PE, it was significantly up-regulated at $10^{-8}$M, $10^{-9}$M, $10^{-11}$M and $10^{-12}$M, but not for $10^{-10}$M. While at 2h PE, it was found to be significantly up-regulated for every dose tested (Fig 7 d-f).

*β (1,3) D glucan* – At 30m PE, Vegfa was significantly down-regulated at $10^{-8}$M. It was found to be significantly down-regulated at both $10^{-8}$M and $10^{-11}$M. Vegfa was significantly up-regulated at 2h PE for $10^{-8}$M, $10^{-9}$M and $10^{-10}$M (Fig 7 g-i).

5) Cdknlb

*Neoechinulin A* – At both 30m and 1h PE, Cdknlb was significantly up-regulated for every dose tested. At 2h PE, it was significantly up-regulated at $10^{-8}$M, $10^{-10}$M, $10^{-11}$M and $10^{-12}$M, but not at $10^{-9}$M (Fig 8 a-c).

*Neoechinulin B* – Cdknlkb was found to be significantly up-regulated at 30m PE for $10^{-8}$M, $10^{-10}$M, $10^{-11}$M and $10^{-12}$M, but not at $10^{-9}$M. At 1h and 2h PE, Cdknlb was found to be significantly up-regulated for every dose tested (Fig 8 d-f).

*β (1,3) D glucan* – Cdknlb was significantly down-regulated at $10^{-8}$M and $10^{-10}$M after 30m PE. At 1h PE, Cdknlb was significantly down-regulated at $10^{-8}$M. At 2h PE, it was significantly up-regulated at $10^{-9}$M, $10^{-10}$M and $10^{-12}$M (Fig 8 g-i).

6) Cd5

*Neoechinulin A* – At 1h and 2h PE, Cd5 was found to be significantly re-regulated at $10^{-8}$M, $10^{-9}$M, $10^{-10}$M and $10^{-11}$M, but not for $10^{-12}$M. Cd5 was not significantly changed at 30m PE for any dose tested (Fig 9 a-c).

*Neoechinulin B* – At 30m PE, Cd5 was significantly up-regulated at $10^{-10}$M and $10^{-11}$M. At 1h PE, it was significantly up-regulated at each concentration tested. At 2h PE, Cd5 was significantly up-regulated at $10^{-9}$M, $10^{-10}$M and $10^{-11}$M (Fig 9 d-f).

*β (1,3) D glucan* – Cd5 was significantly up-regulated at 30m PE for $10^{-10}$M. At 1h PE, Cd5 was significantly up-regulated at $10^{-11}$M and $10^{-12}$M. At 2h PE, Cd5 was significantly up-regulated at $10^{-9}$M and $10^{-12}$M (Fig 9 g-i).

7) Dectin-1

*Neoechinulin A* – At 30m PE, Dectin-1 was found to be significantly up-regulated for $10^{-10}$M and $10^{-12}$M. It was found to be significantly up-regulated at 1h PE for $10^{-10}$M, $10^{-11}$M and $10^{-12}$M. Dectin-1 was significantly up-regulated at 2h PE for all doses tested (Fig 10 a-c).

*Neoechinulin B* - Dectin-1 was found to be significantly up-regulated at 1h PE for $10^{-9}$M and $10^{-11}$M. It was significantly up-regulated at 2h PE for $10^{-9}$M, $10^{-10}$M, $10^{-11}$M and $10^{-12}$M but not $10^{-8}$M. It was not found to be significantly changed at 30m PE for any dose tested (Fig 10 d-f).

*β (1,3) D glucan* – At 1h PE, Dectin-1 was significantly up-regulated for $10^{-9}$M, $10^{-10}$M, $10^{-11}$M and $10^{-12}$M but not $10^{-8}$M. At 2h PE, it was significantly down-regulated at $10^{-8}$M and up-regulated at $10^{-9}$M, $10^{-10}$M and $10^{-11}$M. Dectin-1 was not significantly changed at 30m PE for any dose tested (Fig 10 g-i).

### 2.3.4 Time dependant experiments

For time-dependent experiments, AMs were exposed to neoechinulin A & B and β (1,3) D glucan at a constant concentration of $10^{-8}$M. Experiments were conducted at 30m, 1h, and 2h exposures.

1) Neoechinulin A

AMs exposed to $10^{-8}$M neoechinulin A for the three time points showed significant ($p \leq 0.05$) up-regulation for all genes studied. Significantly ($p \leq 0.05$) up-regulated genes at 30m post exposure (PE) were Icam1, Vegfa and Cdknlb. At 1h PE, significantly ($p \leq 0.05$) up-regulated genes were Bmp2, Hspb1, Icam1, Vegfa, Cdknlb, and Cd5. At 2h PE, Icam1, Vegfa, Cdknlb, Cd5 and Dectin-1 were significantly ($p \leq 0.05$) up-regulated. The time-dependent pattern of expression for most genes assayed was up-regulation at each time tested with the greatest increase of gene expression at 1 h PE. For Cd5, the pattern is different with the same level of increased expression after 1h and 2h exposure. For

Dectin-1 the time-dependent pattern is also different showing the greatest increase in gene expression at 2h PE (Fig 11a).

2) Neoechinulin B

AMs exposed to $10^{-8}$M neoechinulin B for the three time points showed significant ($p \leq 0.05$) up-regulation for 6 of the 7 genes studied. At 30 m PE Icam1, Vegfa, and Cdknlb were significantly ($p \leq 0.05$) up-regulated. Significantly up-regulated genes at 1 h PE were Bmp2, Hspb1, Icam1, Vegfa, Cdknlb, and Cd5. At 2h PE, Icam1, Vegfa, and Cdknlb were significantly up-regulated. The time-dependent pattern of expression for most genes assayed was up-regulation at each time tested with the greatest increase of gene expression at 1 h PE. The only significant difference between the patterns of expression for both neoechinulin A and B is Cd5 (Fig 11b).

3) β (1,3) D glucan

AMs exposed to $10^{-8}$M β (1,3) D glucan for revealed that 6 of the 7 genes studied exhibited significant ($p \leq 0.05$) regulation. At 30m PE, significantly down-regulated genes were Hspb1, Vegfa and Cdknlb. At 1h PE, Bmp2, Icam1, Vegfa and Cdknlb showed significant ($p \leq 0.05$) down-regulation while significant ($p \leq 0.05$) up-regulation was exhibited by Vegfa at 2h PE. Dectin-1 was significantly ($p \leq 0.05$) down-regulated at 2h PE. The time-dependent pattern of expression for most genes assayed was down-regulation at 30 m and 1 h PE, followed by up-regulation after 2 h PE (Fig 12).

### 2.3.5 Cytotoxicity Experiment

AMs were exposed to neoechinulin A, neoechinulin B, β (1,3) D glucan, and diluent controls for 2h. Thereafter, an MTT assay was performed to assess toxicity of these compounds. Results show that neoechinulin B is cytotoxic to RAW 264.7 cells in culture at all doses tested ($p < 0.001$) compared to diluent control. Neoechinulin A and β (1,3) D glucan were not found to be cytotoxic to RAW 264.7 cells in culture at any doses tested (Fig 13).

## 2.4 Discussion

The role of alveolar macrophages (AMs) at the molecular level in modulating inflammation in toxin treated lungs using an *in vitro* model of lung disease was examined in this study. In this study, transduction pathways involved in the acute modulation of acute inflammation were identified. Results indicate that AMs are sensitive to both neoechinulin A & B as well as β (1,3) D glucan. These results support previous studies by DiPenta (2008) who showed that primary AMs are activated by both neoechinulin A and B as well as β (1,3) D glucan and by Kataoka *et al.* (2002) who showed that β (1,3) D glucan activates RAW 264.7 cells. These results are also supported by recent *in vivo* studies by Miller *et al.* (2009) and Rand *et al.* (2009) investigated the effect of mycotoxins and curdlan on mouse lungs. Mice were intratracheally instilled with a dose of $10^{-5}$M of either atranone C, brevianamide, cladosporin, mycophenolic acid, neoechinulin A & B, sterigmatocystin or TMC-120A or a $10^{-6}$M dose of curdlan. Immunohistological and PCR based analyses were performed and it was revealed that mouse lungs exposed to either mycotoxin or curdlan showed evidence of inflammation

such as up-regulation of inflammatory genes as well as expression of dectin-1, MIP-2 and TNF on the in bronchiolar epithelium, alveolar macrophages (AMs), and alveolar type II cells (ATIIs).

Although the neoechinulins have been associated with building-related health problems, to date no information exists regarding the specific mechanisms for their activity in the system. Furthermore, very little information exists regarding the molecular basis of their activity. Therefore, the findings of this study will aid greatly in identifying the mechanisms by which mycotoxins effect gene expression in AMs.

This study has shown that compared to controls, 7 of 18 transduction pathway genes were significantly modulated after RAW cells were exposed to the three low molecular weight compounds tested in this study, and in at least 1 time-point. These were bone morphogenic protein 2 (Bmp2), heat shock protein (Hspb1), intercellular adhesion molecule 1 (Icam1), vascular endothelial growth factor A (Vegfa), cyclin dependent kinase inhibitor (p27) (Cdkn1b), lymphocyte antigen (Cd5) and dectin-1. These genes correspond to the following pathways, respectively; Hedgehog, stress, phospholipase c, NFkB, Wnt, TGF-β, and NFAT. Of these 7, only 4 are directly involved in the inflammatory response. The remaining 3 were still examined in order to broaden our knowledge of the mechanisms behind mycotoxin exposure.

Bone morphogenetic proteins (BMPs) have an essential role in organogenesis and tissue repair. This suggests that BMPs may play an important role in airway remodeling. They are known to be involved in basal airway homeostasis and that there is an accessible reservoir of ligand that can be activated on demand. There are few studies that

look at the role of BMP ligands and their signaling pathways in airway inflammatory processes. Fukui *et al.* (2003) showed that Bmp2 expression is activated by the proinflammatory cytokines IL-1 and TNF-α. Other BMPs (specifically Bmp7) has been shown to modulate the inflammatory response in such ways as inhibiting macrophage trafficking and IL-6 expression, and modulating TNF-α-induced proinflammatory gene expression (Gould *et al.*, 2002). The hedgehog signaling pathway participates in the development of numerous tissues and organs (McMahon *et al.*, 2003). A well known effect of reduced hedgehog signaling in human embryos is cyclopia (the formation of only one eye). In adults, hedgehog signaling directs the formation of certain stem- and precursor-cell populations (Machold *et al.*, 2003). It has been found that increased hedgehog signaling in some organs can lead to cancers- of the skin, cerebellum, muscle, digestive tract, pancreas or prostate (Pasca di Magliano and Hebrok, 2003).

Vegfa is in the Vegf family of proteins and is implicated in vascular remodeling during embryogenesis, tissue regeneration and carcinogenesis (Shibuya, 2001; Tammela *et al.*, 2005; Coultas *et al.*, 2005). Research has shown that hedgehog, Wnt and TGF-β network together during embryogenesis, tissue regeneration and carcinogenesis (Katoh, 2002; Hooper and Scott, 2005). Hedgehog and Wnt signaling have distinct features, but are also sufficiently similar and share enough components to indicate that some aspects of the two pathways might have common evolutionary origins. Both pathways are activated by seven transmembrane receptors. Both pathways use accessory transmembrane protein to regulate the receptor (Nusse, 2003).

Heat shock proteins (HSPs) function as molecular chaperones. They ensure correct folding of proteins into their three-dimensional forms which is crucial for

biological activity in the cell or promote degradation of the misfolded proteins and regulate cell growth and cell signaling pathways that initiate repair, allow adaptation and ensure survival (Lindquist and Craig, 1988; Benjamin and McMillan, 1998; Feder and Hofmann, 1999; Agashe and Hartl, 2000). Although the principle function of the HSPs is chaperone activity, it has been proposed that they have functions in supporting cellular survival under stress conditions by inhibiting apoptosis, stabilization of the cytoskeleton and regulation of cell mobility, migration and muscle contraction. Hspb1, specifically, has a critical role in mediating protection against stress through maintaining normal cell function by stabilizing the cytoskeleton, facilitating repair or removal of damaged proteins, and inhibiting components of both stress and death-receptor induced apoptotic pathways (Bruey *et al.*, 2000; ; Gerthoffer and Gunst, 2001; Sreedhar and Csermely, 2004; Didelot *et al.*, 2006).

Adhesion molecules play integral roles in tumor growth, invasion and metastasis and have also been shown to influence the immune responses to malignant cells (Simmons, 1995). Human intercellular adhesion molecule (Icam1) belongs to the immunoglobulin gene superfamily. Its role has been established as providing signals to immune effector cells (Nishio *et al.*, 1996; Uzendoski *et al.*, 1997) and is known to be extensively upregulated in inflammatory disorders (Montefort and Holgate, 1991). Inflammatory cytokines have been shown to induce the shredding of cell associated Icam1 (Becker *et al.*, 1991) and detection of a soluble form of Icam1 in circulation has been proposed to be a useful marker of inflammation (Seth *et al.*, 1991). The NFkB signaling pathway coordinates the activation of numerous genes in response to pathogens and proinflammatory cytokines (Cohen *et al.*, 1998). NFkB has been demonstrated to

respond to a variety of metabolic stress signals, and protects the cell from undergoing cell death (Royds *et al.*, 1998). Anahid *et al* (2003) have shown that NFkB serves as both positive and negative regulator of Icam1 expression, depending on the stimuli used. Phospholipase C signaling has been shown to be involved in the regulated secretion of neurotrophins (Canossa *et al.*, 2001).

Cyclin dependent kinase inhibitor (p27) (Cdkn1b) is an endogenous cyclin dependent kinase inhibitor (Sherr and Roberts, 1999). The TGF-β signaling pathway inhibits cell proliferation by upregulation of Cdkn2b, Cdknla and Cdkn1b (Massague *et al.*, 2000). Transforming growth factor β (TGF-β) is a potent growth inhibitor for a wide variety of cells including immune lymphocytes. Perturbations of the TGF-β signaling pathway can result in loss of cell growth regulation (Roberts and Sporn, 1990; Miyazono *et al.*, 1994).

Cd5 (lymphocyte antigen) is a 67 kDa membrane protein that requires activation by NFAT signaling (Teutsch *et al.*, 1995). Berland and Wortis (1998) have shown that Cd5 expression in B cells requires activation by NFAT. Nuclear factor of activated T cell (NFAT) signaling is stimulated by an increase in intracellular $Ca^{2+}$. This pathway controls the transcription of lymphokine genes (eg., IL-2, IL-3, IL-4, IL-5, IFN and TNF-α), ligand genes (eg., Cd45 and Cd5) and other genes controlling T cell activation, apoptosis and cell cycle regulation (Serfling *et al.*, 2000).

Classical dose-dependent-like responses in gene expression levels were apparent in cells exposed to neoechinulin B and β (1,3) D glucan. With a classical response, one would expect was the concentration of the compound increases gene expression decreases. Trends for this type of response were seen with Vegfa and Hspb1after 2h

exposure. Evidence for a classical dose-response response was seen in Cd5 and Dectin-1 after 2h exposure to neochinulin B. Non-classical dose-dependent-like responses were apparent in cells exposed to neoechinulin A. This type of response is the opposite of a classical response; when the concentration of the compound decreases gene expression increases. Again, trends were seen especially for Hspb1 after 1h exposure. Evidence for this non-classical dose-response was seen in Dectin-1 after both 1h and 2h exposure to neoechinulin A. However, dose-dependent-like Bmp2 and Hspb1 up-regulated expression was apparent in cells exposed to high concentration ($10^{-8}$ M) neoechinulin B at 1 h PE and at $10^{-9}$ and $10^{-10}$ M concentrations at 2 h PE. For β (1,3) D glucan, dose dependency was manifest as down-regulated Bmp2 expression in cells exposed to 10-8 and 10-9 M curdlan at 1 h PE. It was also apparent in dectin 1 expression in curdlan exposed cells at 1 and 2 h PE.

It is evident that signal transduction pathway activation by neoechinulin A & B and β (1,3) D glucan exhibit time dependency. A number of other studies have demonstrated that responses activated by fungal compounds are time dependent. Alveolar Type II cells exposed to *S. chartarum* and *Penicillium chrysogenum* purified toxins showed different patterns of gene expression showing time-dependence for surfactant proteins and inflammatory genes (Robbins, 2007). This same outcome was seen when AMs were also exposed to purified mycotoxins (DiPenta, 2008). DiPenta (2008) showed rapid, and significant changes in a variety of inflammatory and cell stress-associated genes (within 2h PE) in AMs exposed to neoechinulins A and B, sterigmatocystin, brevianimide and cladosporin at concentrations of $10^{-7}$ and $10^{-8}$M. The downstream effect of signal transduction pathways are changes in gene expression, cell survival, apoptosis

and activation of inflammatory mediators. Therefore, results from DiPenta (2008) would indicate that transduction pathway activation would similarly exhibit time dependent responses. Time dependent changes in transduction pathway activation associated with exposure to fungal compounds is poorly understood. It is interesting that modulation of the genes studied here was rapid (within 30m PE). This suggests heightened sensitivity and an acute response of RAW 264.7 cells to neoechinulin A and B and the β (1, 3) glucan, curdlan.

This study has shown that neoechinulin B is cytotoxic at the doses tested in RAW 264.7 cells. It was found that both neoechinulin A and β (1,3) glucan, however, were non cytotoxic at any doses tested to RAW 264.7 cells. There is evidence showing different levels of cytotoxic effects of many other mycotoxins. Trichothecenes were examined for their cytoxotic properties and it was found that type B trichothecenes such as vomitoxin and nivalenol were not cytotoxic at the concentrations examined, whereas satratoxin F, satratoxin H and T-2 were moderately toxic. In contrast, satratoxin G, roridin A, and verrucarin A were highly cytotoxic (Yang et al., 2000). These findings along with the findings of Yang et al (2000), support the idea that one species of fungus can produce various types of mycotoxins with varying degrees of cytotoxicity.

One objective of this study was to determine the "no observed adverse effect" level (NOAEL). Doses ranging from $10^{-8}$M to $10^{-12}$M were used in this study and effects were still seen in as gene expression changes in AMs after exposure to $10^{-12}$M solutions of neoechinulin A, B and β (1, 3) glucan. The amount of neoechinulin A or B in the spore has not yet been quantified; however this has been determined for some mycotoxins. It has been reported that both *Aspergillius fumigatus* and spores of some *Stachybotrys*

*chartarum* isolates contain in the order of $10^{-5}$M of fumitremorgen A, B and C and satratoxin G, respectively (Fisher et al., 2000; Sorenson et al., 1987). It is apparent from the results of this study is that the NOAEL varied depending on the compound tested, the gene evaluated and the end time point. In general, both neoechinulin A and B showed similar trends, especially at 1h PE. At this time point, the NOAEL for Vegfa, Icam-1 and Cdkn1b was less than $10^{-12}$M in exposed RAW 264.7 cells. However, for Bmp2 it was $10^{-12}$M for neoechinulin A and $10^{-9}$M for neoechinulin B. For Hspb1 it was less than $10^{-12}$M for neoechinulin A and $10^{-12}$M for neoechinulin B. For Cd5 the NOAEL was less than $10^{-12}$M for neoechinulin A and $10^{-12}$M for neoechinulin B exposed cells. For β (1,3) D glucan exposed cells, the NOAEL ranged from less than $10^{-12}$M for Cd5, Dectin-1 and Cdkn1b, $10^{-11}$M for Vegfa, $10^{-10}$M for Icam1 and $10^{-9}$M for Bmp2 to $10^{-8}$M Hspb1. These results are interesting because they point to the importance of using the responses of multiple genes as a means of evaluating the NOAEL. While not explicitly stated in their studies, Miller *et al.* (2009) and Rand *et al.* (2009) also showed similar results. For example, in their study of inflammatory gene expression in mouse lungs stimulated by curdlan, only a few of 83 genes were significantly up-regulated at $10^{-10}$M concentration and at 4h but not at 12h PE while at higher concentrations many more genes were expressed at both time points.

Chapter 3 – The effects of interactions between neoechinulin A and β (1,3) D glucan on AM signal transduction pathway activation.

3.1 Introduction

*Eurotium amstelodami* is commonly found in indoor environments that suffer from water damage (Flannigan and Miller, 2001; Miller *et al.*, 2008). Neoechinulin A & B have been identified as major secondary metabolites of this filamentous fungus (Slack *et al.*, 2009).

In indoor environments, mold growth is associated with both allergenic and non-allergenic effects on population health (NAS, 2004; Health Canada, 2004; WHO, 2004). Most species of fungi that grow on moist building materials produce spores that contain relatively high concentrations of mycotoxins, species-specific allergens and proteases bound by a cell wall made of β (1, 3) D-glucan (Rand, 2007).

In building environments, humans may be exposed to both mycotoxins and glucans as well as other microbial agents (eg, endotoxin). Fungal spores contain species specific mixtures of mycotoxins, allergens and proteases bound by a cell wall made of β (1, 3) D-glucan (Rand, 2007). Interactions between the different exposures in moisture-damaged buildings are inevitable, since the spores of a single fungal species alone may contain various metabolites, and the moisture-damaged site is a habitat of more than one microbial species (Anderson et al., 1997; Nielsen et al., 1999; Hyvarinen et al., 2002) Given the widespread occurrence of human exposure to mixtures, these combined effects are of major concern.

Interactions between mycotoxins, glucan, endotoxin, fungal and bacterial spores on cell immune responses have been studied. Studies show synergistic, antagonistic and additive toxicity effects after simultaneous exposures. One study has shown that combinations of *Stachybotrys chartarum* spores with the spores of *Streptomyces californicus* had a clear synergistic effect on the production of an inflammatory mediator (cytokine) in mouse macrophages (Huttunen et al., 2004). Another study showed that after exposure to the spores of co-cultivated *S. californicus* and *S. chartarum* there was a significant influence on the regulation of cell cycle arrest compared to either spore alone (Pettinen et al., 2005). Other studies examining mixtures of mycotoxins also found combination effects that were stronger than one mycotoxin alone (Thuvander et al., 1999; Tammer et al., 2007;). Tammer et al. (2007) applied an established model for immunotoxic studies using stimulated human peripheral blood mononuclear cells (PBMC) and showed that the effects on cytokine production of mixtures of mycotoxins was stronger than the effects caused by the toxins applied singly. A different study, however, showed no synergistic effects, but rather, additive toxicity and antagonistic effects (Thuvander et al., 1999). Human lymphocytes were exposed to a combination of nivalenol and T-2 toxin which resulted in additive toxicity. Interestingly, when T-2 toxin was combined with deoxynivalenol (DON) the result was an inhibition of the proliferative response that was significantly lower than the individual toxins which shows an antagonistic action. Folemark *et al.* (1997) studied the effects of the β (1, 3) D-glucan curdlan on the production of eosinophils in the airways of guinea pigs and determined there was an increase in these cell numbers after exposure to glucan. This effect was seen to decrease after a simultaneous exposure to bacterial endotoxin.

The purpose of this study is to examine the response of RAW 264.7 murine macrophages (RAW 264.7) after simultaneous exposure to neoechinulin A and β (1, 3) D-glucan shown as heightened or depressed gene expression. Based on studies that have shown that the effects of mixtures of mycotoxins were stronger than one mycotoxin alone (Thuvander et al., 1999; Tammer et al., 2007) it is hypothesized that after exposure to two compounds simultaneously, RAW 264.7 cells will have a heightened response shown as increased gene expression.

## 3.2 Materials and Methods

### 3.2.1 Toxins

Neoechinulin A (Fig 1) from *Eurotium amstelodami* was isolated, purified and identified by Dr. David Miller, Department of Chemistry, Carleton University, Ottawa.

Neoechinulin A was dissolved in 1 mL 100% EtOH and then diluted in 100 mL of 10% EtOH, endotoxin free saline (PBS) to a concentration of $10^{-5}$ M. β (1, 3) D-glucan (from J.D. Miller) was dissolved in 1 mL of 0.3 M sodium hydroxide and diluted in 100 mL PBS to $10^{-5}$ M. These were administered to the cell culture simultaneously at doses of $10^{-9}$ and $10^{-10}$M. Neoechinulin A was chosen for this study based on results from chapter two's cytoxicity experiment, in which this mycotoxin is shown to be not cytotoxic to RAW 264.7 murine macrophages in culture.

### 3.2.2 Cell Culture

The RAW 264.7 murine macrophage cell line was obtained from the American Type Cultre Collection (Rockwille, MD, USA). Cells were maintained at 37°C in a 5%

$CO_2$ humidified incubator in RPMI (Invitrogen) medium supplemented with 10% (v/v) heat inactivated fetal bovine serum (FBS, Invitrogen) and 100 U/ml penicillin and 100 μg/ml streptomycin (Sigma). Macrophage cell numbers were assessed using a hemacytometer.

### 3.2.3 Experimental Design

AMs were exposed to both neoechinulin A and β (1,3) D-glucan simultaneously for 30m, 1h and 2h at $10^{-9}$ and $10^{-10}$M concentrations. All experiments were performed in triplicate.

At the end of the desired exposure time, the reactions were stopped by draining the medium and rinsing the flasks with 2ml sterile PBS. Following rinsing, 1.25ml RNAlater® was added to each flask, cells were scrapped into 2ml eppendorf tubes and stored at -80°C.

### 3.2.4 RNA Extraction

Total RNA isolation was performed using RNeasy® mini kit (Qiagen), according to the manufacturer's specifications. Briefly, treatment and control cells were disrupted using Buffer RLT (Qiagen) and homogenized using syringe and needle, per direction. Lysate was precipitated using 70% ETOH followed by centrifugation (at 10,000 rpm for 15 sec) at 4°C in an RNeasy column to collect RNA. The column containing RNA washed in RWI buffer (Qiagen), treated with RNase-free DNase to eliminate DNA contamination according to manufacturer's instructions (Sigma Aldrich), and then washed with RWI followed by RPE buffer (Qiagen) washes. After washing, RNA was

resuspended in RNAse/ DNase free water (Sigma Aldrich. The concentration of RNA in samples was determined using a NanoDrop® ND-1000. Samples with 260/280nm ratio of ≥ 2.0 and a 260/230nm ratio ≥ 1.90 were used for qPCR analysis.

### 3.2.5 Reverse Transcription PCR

Reverse transcription (RT) Polymerase Chain Reaction (PCR) reactions were carried out using a reaction ready first strand cDNA synthesis kit (C-03 SuperArray, Bioscience Corp®) according to manufacturer's instructions. An annealing mix was prepared first by combining 1μg of RNA with 2μL of GE Buffer (5x genomic DNA elimination buffer), the final volume was adjusted to 10μL with RNase-free water. This annealing mix was preheated at 42°C for 5 minutes then combined with a RT cocktail (4μL 5x RT buffer (BC3), 1μL primer and external control mix (P2), 2μL RT enzyme (RE3), and 3μL of RNase-free water). The RT reaction was performed; 42°C for 5 minutes, followed by heating at 95°C for 5 minutes to degrade the RNA and inactivate the RE3. All cDNA was stored at -20°C.

### 3.2.6 Real-time PCR

Forward and reverse PCR primers (Table 3) for the genes of interest (Table 2) were designed using Primer 3 and custom synthesized by Integrated DNA Technologies. The q PCR protocol (Figure 4) was carried out on an ABI Prism 7000 Sequence Detection System® (Applied Biosystems). A two-step cycling program q PCR reaction was performed. The first step was 10 minutes at 95°C to activate the hotstart DNA polymerase, next there were 40 cycles for amplification starting at 95°C for 15 seconds,

and then the temperature was lowered to 55°C for 60 seconds in order to detect SYBR green fluorescence.

Relative gene expression was determined according to the comparative $C_t$ method, with the Actb housekeeping gene and diluent control references set as the calibrators. Fold change equals $2^{\Delta\Delta Ct}$, where the $C_t$ is the threshold cycle, $\Delta C_t$ is the difference between the $C_t$ values of the target gene and the internal control gene, $\Delta\Delta C_t$ represents the difference between the $\Delta C_t$ value for the control cells and treated cells.

### 3.2.7 Statistical Analysis

A Shapiro-Wilk test for normality was performed to verify if the samples were normally distributed. Data (n=3) were then tested for statistical significance using two-way analysis of variance (ANOVA). Bonferroni post test was also used to examine differences between control and treatment gene expression data. Statistical analysis was carried out using Graph Pad Prism version 4.0 and results were considered significant at $\alpha \leq 0.05$ (Gotelli and Ellison, 2004). For graphical representation data was log transformed. For detailed ANOVA tables the reader is referred to appendix IV.

## 3.3 Results

### 3.3.1 Neoechinulin A + β (1,3) D-glucan vs. neoechinulin A or β (1,3) D-glucan

RAW 264.7 murine macrophages were exposed to both neoechinulin A and β (1,3) D-glucan simultaneously at $10^{-9}$ and $10^{-10}$M concentrations. These experiments were conducted at 30m, 1h, and 2h time periods. This study was compared to results of gene expression changes by either neoechinulin A or β (1,3) D-glucan alone.

Bmp2

The simultaneous exposure to $10^{-10}$M neoechinulin A and β (1,3) D-glucan was significantly ($p \leq 0.05$) reduced than that of neoechinulin A alone after 1h post exposure (PE) (Fig 15a).

Hspb1

The simultaneous exposure to $10^{-10}$M neoechinulin A and β (1,3) D-glucan was significantly ($p \leq 0.05$) reduced than that of neoechinulin A alone after 1h post exposure (PE) (Fig 15b).

Icam1

The simultaneous exposure to $10^{-9}$M neoechinulin A and β (1,3) D-glucan was significantly ($p \leq 0.05$) increased than that of neoechinulin A or β (1,3) D-glucan alone after 2h post exposure (PE). It was also significantly greater than that of β (1,3) D-glucan alone at 30m, 1h and 2h PE at both $10^{-9}$M and $10^{-10}$M (Fig 14c and Fig 15c).

Vegfa

AMs exposed to simultaneous doses of neoechinulin A and β (1,3) D-glucan was found to elicit significantly greater responses than that of β (1,3) D-glucan alone at 1h and 2h PE for $10^{-9}$M (Fig 14d) and at 30m, 1h and 2h PE for $10^{-10}$M (Fig 15d).

Cdknlb

There is an increased response in AMs after a simultaneous dose of neoechinulin A and β (1,3) D-glucan when compared to just β (1,3) D-glucan alone at 1h PE for $10^{-9}$M (Fig 14e) and at 30m and 1h PE for $10^{-10}$M (Fig 15e).

Cd5

There is no significant change in gene expression for Cd5 when RAW 264.7 murine macrophages are exposed to either a simultaneous dose of $10^{-9}$M neoechinulin A and β (1,3) D-glucan or neoechinulin A or β (1,3) D-glucan alone, however at a simultaneous dose of $10^{-10}$M, AMs show an increased response at 1h PE (Fig 14f and Fig 15f).

Dectin-1

There is a significant increase in gene expression for Dectin-1 when AMs are exposed to a simultaneous dose of neoechinulin A and β (1,3) D-glucan compared to just β (1,3) D-glucan alone after 2h PE for both doses tested (Fig 14g and Fig 15g).

## 3.4 Discussion

This study examined the potential interactions between neoechinulin A and β (1,3) D-glucan on signal transduction pathway activation in RAW 264.7 murine macrophages (AMs). This study was conducted at 30m, 1h and 2h PE and at doses of $10^{-9}$ and $10^{-10}$M.

Interactions between mycotoxins and spores have been reported in past studies. One study has shown that exposures of combinations of *Stachybotrys chartarum* spores with the spores of *Streptomyces californicus* had a clear synergistic effect on the production of an inflammatory mediator (cytokine) in mouse macrophages (Huttunen et al., 2004). Another study revealed that exposure to the spores of co-cultivated *S. californicus* and *S. chartarum* had a significant influence on the regulation of cell cycle arrest (Penttinen et al., 2005). Other studies examining mixtures of mycotoxins also found combination effects that were stronger than one mycotoxin alone. These effects

were synergistic, antagonistic and additive toxicity effects (Thurvander et al., 1999; Tammer et al., 2007).

This study shows that after 1h exposure to a simultaneous dose of $10^{-10}$M neoechinulin A and β (1,3) D-glucan, there is an antagonistic response of Bmp2 and Hspb1 (Fig 15). After 2h PE Icam1 shows clear synergistic response when RAW 267.4 cells are exposed to a simultaneous dose of $10^{-9}$M neoechinulin A and β (1,3) D-glucan. For the other genes tested, however, there doesn't seem to be any statistically significant evidence of a synergistic interaction between neoechinulin A and β (1,3) D-glucan (Fig 14 & 15). There are trends at 2h PE for Bmp2, Hspb1, Vegfa, Cdknlb, Cd5 and dectin-1 showing a synergistic interaction; however these were not statistically significant. From results of chapter 2, we see that generally when AMs were exposed to neoechinulin A alone (Fig 11a), gene expression was greater than when exposed to β (1,3) D-glucan alone (Fig 12). The results from this study suggest that there may be a masking effect for some genes when RAW 267.4 cells are exposed to both neoechinulin A and β (1,3) D-glucan. However, the nature of this effect remains unclear and should be explored in future studies.

This study shows statistical evidence that simultaneous exposure of RAW 264.7 cells to neoechinulin A and β (1,3) D-glucan at $10^{-9}$M resulted in elevated Icam1, Vegfa and Dectin-1 expression after 2h PE (Fig 14) compared to expression in cells exposed to these compounds individually This effect was also seen at $10^{-10}$M for Icam1, Cdknlb and Dectin-1 and at as early as 1h PE (Icam1). This result supports the hypothesis that exposure to a mixture of compounds elicits a synergistic interaction. At a concentration of $10^{-10}$M significantly increased Bmp2 and Hspb1 expression (Fig 15) was observed in

cells exposed to single compounds compared to mixed ones. This antagonistic result is interesting because it supports the study by Thurvander *et al.* (1999) who also showed antagonistic responses of mixtures on human lymphocytes.

These findings highlight the important modulatory effect that mixtures of compounds at low concentration have on gene expression. Furthermore, that mycotoxin and glucan interactions must be carefully considered when evaluating the possible health effects associated with exposure to moisture and mold damaged buildings.

## Chapter 4

### 4.1 General Conclusions

Little information is known about the molecular mechanisms responsible for immune responses caused by metabolites of *Eurotium amstelodami*, neoechinulin A and B. *Eurotium amstelodami* is a xerophilic species commonly recovered from damp building materials. The majority of published literature to date focuses on the impact of mesophilic and hydrophilic species' metabolites on respiratory health.

The objectives of this study were three fold; 1) Identify which transduction pathways are activated in RAW 264.7 murine macrophages (AMs) following mycotoxin and glucan exposure, 2) determine if there is time- and/or dose- dependency, and 3) identify any interactions between mycotoxin and glucan.

This study has shown that after exposure to neoechinulin A, B or β (1,3) glucan RAW 264.7 cells express genes for the following pathways; Hedgehog, phospholipase c, NFkB, Wnt, TGF-β, and a stress pathway. Although this study focused on the mechanisms of the immune response, it was an interesting find that these mycotoxins and

curdlan also activate signal transduction pathways that are involved in pathways that are not involved in the immune response, such as embryonic development (ie, Hedgehog pathway). Up- and/or down-regulation of these genes may have detrimental effects on a developing embryo in utero, or young individuals who may be exposed to molds growing in damp building environments. The results of this study show that the impact of mycotoxins is broader than inflammation alone; the reactions are associated with embryogenesis, tissue regeneration, apoptosis and carcinogenesis which support the notion that there is a much broader range of effects that require further investigation.

This study has shown that activation of signal transduction pathways is a time-dependent phenomenon. Results from this study show that the NOAEL is not only dependent on the gene tested but on the end time point as well.

In addition to determining the effects of neoechinulin A and β (1,3) glucan on AMs alone, the final objective of this study was to determine if there were any interactions between neoechinulin A and β (1,3) glucan seen as heightened or depressed gene expression. A clear synergistic effect was seen at both doses tested for Icam1, Vegfa, Cdknlb and Dectin-1 at 2h PE. For Bmp2 and Hspb1 after 1h PE there is evidence of an antagonistic interaction. When exposed to both compounds simultaneously there is a reduced response compared to the effect of either of the compounds alone. However with the other genes tested, the simultaneous exposure is masked by the expression of neoechinulin A alone.

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Table 1 – Description of transduction pathway focused genes and housekeeping genes (Adapted from SA Biosciences # PAMM-014)

| Gene Name | Ref Sequence | Description | Transduction Pathway (s) |
|---|---|---|---|
| Atf2 | NM_009715 | Activating transcription factor 2 | Stress |
| Bax | NM_007527 | Bcl2-associated X protein | p53 |
| Bcl2 | NM_009741 | B-cell leukemia/lymphoma 2 | P13 kinase, AKT, Jak/Src, estrogen |
| Bcl2l1 | NM_009743 | Bcl2-like 1 | Jak/Src, phospholipase c |
| Birc1a | NM_008670 | Baculoviral IAP repeat containing 1a | NFkB |
| Birc2 | NM_007465 | Baculoviral IAP repeat containing 2 | NFkB |
| Birc3 | NM_007464 | Baculoviral IAP repeat containing 3 | NFkB |
| Birc5 | NM_009689 | Baculoviral IAP repeat containing 5 | Wnt |
| Bmp2 | NM_007553 | Bone morphogenetic protein 2 | Hedgehog |
| Bmp4 | NM_007554 | Bone morphogenetic protein 4 | Hedgehog |
| Brca1 | NM_009764 | Breast cancer 1 | estrogen |
| Ccl2 | NM_011333 | Chemokine (C-C motif) ligand 2 | LDL |
| Ccl20 | NM_016960 | Chemokine (C-C motif) ligand 20 | NFkB |
| Ccnd1 | NM_007631 | Cyclin D1 | Wnt, P13 kinase, AKT |
| Cd5 | NM_007650 | CD5 antigen | NFAT |
| Cdh1 | NM_009864 | Cadherin 1 | Wnt |
| Cdk2 | NM_016756 | Cyclin-dependent kinase 2 | androgen |
| Cdkn1a | NM_007669 | Cyclin-dependent kinase inhibitor 1A (P21) | TGF-B, p53, androgen |
| Cdkn1b | NM_009875 | Cyclin-dependent kinase inhibitor 1B | TGF-B |
| Cdkn2a | NM_009877 | Cyclin-dependent kinase inhinitor 2A | TGF-B |
| Cdkn2b | NM_007670 | Cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4) | TGF-B |
| Cebpb | NM_009883 | CCAAT/enhancer binding protein (C/EBP), beta | Insulin |
| Csf2 | NM_009969 | Colony stimulating factor 2 (granulocyte-macrophage) | Calcium and protein kinase c, LDL |
| Cxcl1 | NM_008176 | Chemokine (C-X-C motif) ligand 1 | NFkB |
| Cxcl9 | NM_008599 | Chemokine (C-X-C motif) ligand 9 | Jak/stat |
| Cyp19a1 | NM_007810 | Cytochrome P450, family 19, subfamily a, polypeptide 1 | Creb |
| Egr1 | NM_007913 | Early growth response 1 | Mitogenic, Creb, phospolipase c |

| | | | |
|---|---|---|---|
| Ei24 | NM_007915 | Etoposide induced 2.4 mRNA | p53 |
| En1 | NM_010133 | Engrailedm1 | Hedgehog, Retinoic Acid |
| Fas | NM_007987 | Fas (TNF receptor superfamily member) | p53 |
| Fasl | NM_010177 | Fas ligand (TNF superfamily member 6) | NFAT |
| Fasn | NM_007988 | Fatty acid synthase | Insulin |
| Fgf4 | NM_010202 | Fibroblast growth factor 4 | Wnt |
| Fn1 | NM_010233 | Fibronectin 1 | P13 kinase, AKT |
| Fos | NM_010234 | FBJ osteosarcoma oncogene | Mitogenic, Stress, creb, calcium protein kinase c, phospholipase c |
| Foxa2 | NM_010446 | Forkhead box A2 | Hedgehog |
| Gadd45a | NM_007836 | Growth arrest and DNA-damage-inducible 45 alpha | p53 |
| Greb1 | NM_015764 | Gene regulated by estrogen in breast cancer production | estrogen |
| Gys1 | NM_030678 | Glycogen synthase 1, muscle | Insulin |
| Hhip | NM_020259 | Hedgehog-interacting protein | Hedgehog |
| Hk2 | NM_013820 | Hexokinase 2 | Insulin |
| Hoxa1 | NM_010449 | Homeo box A1 | Retinoic Acid |
| Hsf1 | NM_008296 | Heat shock factor 1 | Stress |
| Hspb1 | NM_013560 | Heat shock protein 1 | Stress |
| Icam1 | NM_010493 | Intercellular adhesion molecule | NFkB, phospholipase c |
| Igfbp3 | NM_008343 | Insulin-like growth factor binding protein 3 | p53 |
| Igfbp4 | NM_010517 | Insulin-like growth factor binding protein 4 | estrogen |
| Ikbkb | NM_010546 | Inhibitor of kappaB kinase beta | NFkB |
| Il1a | NM_010554 | Interleukin 1 alpha | NFkB |
| Il2 | NM_008366 | Interleukin 2 | NFkB, NFAT, Calcium and protein kinase c |
| Il2ra | NM_008367 | Interleukin 2 receptor, alpha chain | Calcium and protein kinase c |
| Il4a | NM_001008700 | Interleukin 4 receptor, alpha | Jak/stat |
| Irf1 | NM_008390 | Interferon regulatory factor 1 | Jak/stat |
| Jun | NM_010591 | Jun oncogene | Mitogenic, Wnt, P13 kinase, AKT, Calcium protein kinase c, phospholipase c |

| | | | |
|---|---|---|---|
| Lef1 | NM_010703 | Lymphoid enhancer binding factor 1 | Wnt |
| Lep | NM_008493 | Leptin | Insulin |
| Lta | NM_010735 | Lymphotoxin A | NFkB |
| Mdm2 | NM_010786 | Transformed mouse 3T3 cell double minute 2 | p53 |
| Mmp10 | NM_019471 | Matrix metallopeptidase 10 | Jak/stat |
| Mmp7 | NM_010810 | Matrix metallopeptidase 7 | p13 kinase, AKT |
| Myc | NM_010849 | Myelocytomatosis oncogene | Wnt, P13 kinase, AKT, stress, calcium and protein kinase c |
| Nab2 | NM_008668 | Ngfi-A binding protein 2 | Mitogenic |
| Nfkbia | NM_010907 | Nuclear factor of kappa light chain gene enhancer in B-cells inhibitor, alpha | NFkB |
| Nos2 | NM_010927 | Nitric oxide synthase 2, inducible, macrophage | NFkB, Jak/stat, calcium and protein kinase c, phospholipase c |
| Nrip1 | NM_173440 | Nuclear receptor interacting protein 1 | estrogen |
| Odc1 | NM_013614 | Ornithine decarboxylase, structural 1 | Calcium and protein kinase c |
| Pparg | NM_011146 | Peroxisome proliferator activated receptor gamma | Wnt |
| Ptch1 | NM_008957 | Patched homolog 1 | Hedgehog |
| Ptgs2 | NM_011198 | Prostoglandin-endoperoxide synthase 2 | phospholipase c |
| Rbp1 | NM_011254 | Retinol binding protein 1, cellular | Retinoic Acid |
| Sele | NM_011345 | Selectin, endothelial cell | LDL |
| Selp | NM_011347 | Selectin, platelet | LDL |
| Tank | NM_011529 | TRAF family member-associated Nf-kappa B activator | NFkB |
| Tcf7 | NM_009331 | Transcription factor 7, T-cell specific | Wnt |
| Tert | NM_009354 | Telomerase reverse transcriptase | NFkB |
| Tfrc | NM_011638 | Transferrin receptor | Calcium and protein kinase c |
| Tmepai | NM_022995 | Transmembrane, prostate androgen induced RNA | androgen |
| Tnf | NM_013693 | Tumer necrosis factor | NFkB |
| Trp53 | NM_011640 | Transformation related protein 53 | Stress |
| Vcam1 | NM_011693 | Vascular cell adhesion molecule 1 | NFkB, phospholipase c, LDL |
| Vegfa | NM_009505 | Vascular endothelial growth factor A | Wnt |
| Wisp1 | NM_018865 | WNT1 inducible signaling pathway protein 1 | Wnt |

| | | | |
|---|---|---|---|
| Wnt1 | NM_021279 | Wingless-related MMTV integration site 1 | Hedgehog |
| Wnt2 | NM_023653 | Wingless-related MMTV integration site 2 | Hedgehog |
| Gusb | NM_010368 | Glucuronidase, beta | Housekeeping gene |
| Hprt1 | NM_013556 | Hypoxanthine guanine phosphoribosyl transferase 1 | Housekeeping gene |
| Hsp90ab1 | NM_008302 | Heat shock protein 90 kDa alpha (cytosolic), class B member 1 | Housekeeping gene |
| Gapdh | NM_008084 | Glyceraldehyde-3-phosphate dehydrogenase | Housekeeping gene |
| Actb | NM_007393 | Actin, beta, cytoplasmic | Housekeeping gene |

Table 2 – Genes of Interest with their corresponding forward and reverse primer sequences

| Gene Name | Ref Sequence | Forward Sequence | Reverse Sequence |
|---|---|---|---|
| Bmp2 | NM_007553 | GCTCCACAAACGAGAAAAGC | AGCAAGGGGAAAAGGACACT |
| Hspb1 | NM_013560 | CCTCTTCCCTATCCCCTGAG | TCAAAAGAGCGCACAGATTG |
| Icam1 | NM_010493 | TTCACACTGAATGCCAGCTC | GTCTGCTGAGACCCCTCTTG |
| Vegfa | NM_009505 | CAGGCTGCTGTAACGATGAA | AAATGCTTTCTCCGCTCTGA |
| Cdknlb | NM_009875 | AGCGTTTCTTCATTGCCTGT | CACAAAACATGCCACTTTGG |
| Cd5 | NM_007650 | GTGGCTCCAATTCCAAGTGT | AAGGGGTCACCACATCTCAG |
| Dectin-1 (Clec7a) | NM_020008 | GGAATCCTGTGCTTTGTGGT | GTAGTTTGGGATGCCTTGGA |
| Actb | NM_007393 | AGCCATGTACGTAGCCATCC | TCTCAGCTGTGGTGGTGAAG |

Table 3 – Significantly regulated genes when AMs are exposed to neoechinulin A & B at $10^{-8}$M for 2h: Transduction Pathway Screening Results

| Mycotoxin | GENE | Transduction Pathway |
|---|---|---|
| 2h Neo A 10-8M | Bmp2 | Hedgehog Pathway |
| | Hspb1 | Stress Pathway |
| | Icam1 | Phospholipase c/NFkb Pathways |
| | Vegfa | Wnt Pathway |
| | Cdknlb | TGF-B pathway |
| 2h Neo B 10-8M | Bmp2 | Hedgehog Pathway |
| | Cd5 | NFaT Pathway |

Table 4 – qPCR Reaction Parmeters

| Cycles | Duration | Temperature |
|---|---|---|
| 1 | 10 min | 95°C |
| | 15 sec | 95°C |
| 40 | 1 min | 60°C/55°C |

Table 5 - Summary table for gene regulation changes. Values in red indicate down-regulation. (Significantly ($p \leq 0.05$) regulated genes in bold).

| Fold Regulation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Neoechinulin A | | | Neoechinulin B | | | β (1,3) Glucan | | |
| **Gene** | **30m** | **1h** | **2h** | **30m** | **1h** | **2h** | **30m** | **1h** | **2h** |
| **$10^{-8}$M** | | | | | | | | | |
| Bmp2 | 13.0 | **2466.5** | 4.3 | 22.7 | **1195.0** | 7.7 | -8.0 | **-48.3** | 4.5 |
| Hspb1 | 2.2 | **48.0** | 9.4 | 4.0 | **182.8** | 18.2 | -12.8 | -1.6 | 1.3 |
| Icam1 | **2064.5** | **34233.8** | **728.7** | **905.8** | **18021.9** | **1422.6** | -11.3 | **-389.1** | 2.9 |
| Vegfa | **393.2** | **21964.7** | **1468.4** | **143.8** | **22002.8** | **3540.2** | -14.4 | -12.0 | **36.2** |
| Cdknlb | **229.2** | **5542.7** | **330.8** | **507.5** | **3124.5** | **558.4** | -16.9 | -275.2 | 3.0 |
| Cd5 | 1.5 | **33.7** | **39.1** | 2.4 | **368.1** | 9.2 | -3.2 | -2.2 | -2.6 |
| Dectin-1 | 5.4 | 1.1 | 18.6 | 2.6 | 1.7 | 8.1 | 1.2 | 1.1 | **-438.3** |
| **$10^{-9}$M** | | | | | | | | | |
| Bmp2 | -2.8 | 21.4 | 8.6 | 1.9 | 2.3 | 64.0 | **-8.6** | **-7.2** | 2.1 |
| Hspb1 | 2.6 | **57.5** | 8.6 | 3.5 | 2.3 | **64.0** | 1.4 | 2.6 | 1.4 |
| Icam1 | **1310.7** | **2521.8** | 19.8 | **544.5** | **1915.2** | **1525.0** | -2.1 | 1.9 | 2.0 |
| Vegfa | **149.2** | **2523.8** | **87.1** | 179.4 | **1721.5** | **1951.1** | 1.2 | 1.9 | **11.3** |
| Cdknlb | **83.1** | **184.4** | 8.6 | 9.8 | **1230.7** | **4402.0** | -1.2 | 1.2 | **27.4** |
| Cd5 | 1.4 | 10.6 | 8.6 | 4.1 | **124.7** | **142.1** | 2.7 | 1.1 | 4.3 |
| Dectin-1 | 4.8 | 6.5 | **51.4** | -3.4 | 30.2 | **3817.5** | 2.4 | **60.4** | **5.2** |
| **$10^{-10}$M** | | | | | | | | | |
| Bmp2 | 1.4 | **222.2** | 45.3 | 24.2 | 3.0 | 49.9 | -1.8 | -1.2 | 2.6 |
| Hspb1 | 4.6 | **222.9** | 45.3 | **1243.8** | 3.0 | **33.9** | 1.3 | 2.4 | 2.8 |
| Icam1 | **7340.7** | **1592.6** | **2890.9** | **37289.1** | 2.8 | **3353.9** | -1.3 | -1.1 | 3.4 |
| Vegfa | **344.3** | **2457.3** | **12548.0** | **14080.4** | 5.9 | **591.0** | 1.1 | 1.5 | 6.8 |
| Cdknlb | **176.1** | **817.7** | **354.8** | **7469.5** | **69.3** | **1640.3** | -1.6 | 1.2 | **17.2** |
| Cd5 | 5.6 | **222.9** | **101.7** | **24.3** | **19.7** | **33.3** | 5.4 | 1.1 | 8.1 |
| Dectin-1 | 15.5 | 14.4 | **841.6** | 3.7 | 2.5 | **1116.5** | 3.8 | **91.4** | **6.2** |
| **$10^{-11}$M** | | | | | | | | | |
| Bmp2 | -1.4 | **238.2** | 26.0 | 4.8 | 4.6 | 14.9 | -2.2 | -4.7 | 2.0 |
| Hspb1 | 2.1 | **238.9** | 26.0 | **505.4** | 9.9 | 14.9 | -1.1 | 7.1 | 2.1 |
| Icam1 | **4081.7** | **9339.1** | **833.0** | **24216.5** | **1624.7** | **124.0** | -2.1 | 1.9 | -2.1 |
| Vegfa | **200.5** | **8761.1** | **6288.6** | **9717.9** | **2253.9** | **58.1** | -1.2 | -9.4 | -1.2 |
| Cdknlb | **216.3** | **408.4** | **1418.3** | **10822.9** | **687.2** | **129.4** | 1.1 | -4.5 | 1.4 |
| Cd5 | 2.2 | **238.9** | **84.1** | **22.3** | **68.3** | 14.9 | 3.5 | **59.7** | 3.2 |
| Dectin-1 | 7.5 | 32.9 | **2952.5** | 3.1 | 35.0 | **189.7** | 2.8 | **45.3** | -6.2 |
| **$10^{-12}$M** | | | | | | | | | |
| Bmp2 | 1.9 | 3.0 | 4.6 | 1.1 | 1.6 | 5.3 | -1.7 | 2.8 | 22.1 |
| Hspb1 | 4.7 | 10.8 | 4.6 | 20.8 | 14.4 | 5.3 | 3.5 | 92.0 | 24.3 |
| Icam1 | **1093.3** | **5185.5** | 21.8 | **2395.9** | **4145.2** | 26.8 | -1.2 | 2.9 | 3.6 |
| Vegfa | **70.9** | **5040.8** | **17644.5** | **202.2** | **2006.5** | **60.8** | 1.6 | -4.7 | 5.4 |
| Cdknlb | **122.4** | **1094.3** | **1528.0** | **115.4** | **891.1** | **160.3** | 1.3 | 1.0 | 17.9 |
| Cd5 | 5.8 | 3.0 | 11.6 | 4.0 | **69.2** | 5.6 | 7.6 | **138.0** | **29.0** |
| Dectin-1 | 16.7 | 30.6 | **584.8** | 3.4 | 22.6 | **65.4** | 6.0 | **169.3** | 1.9 |

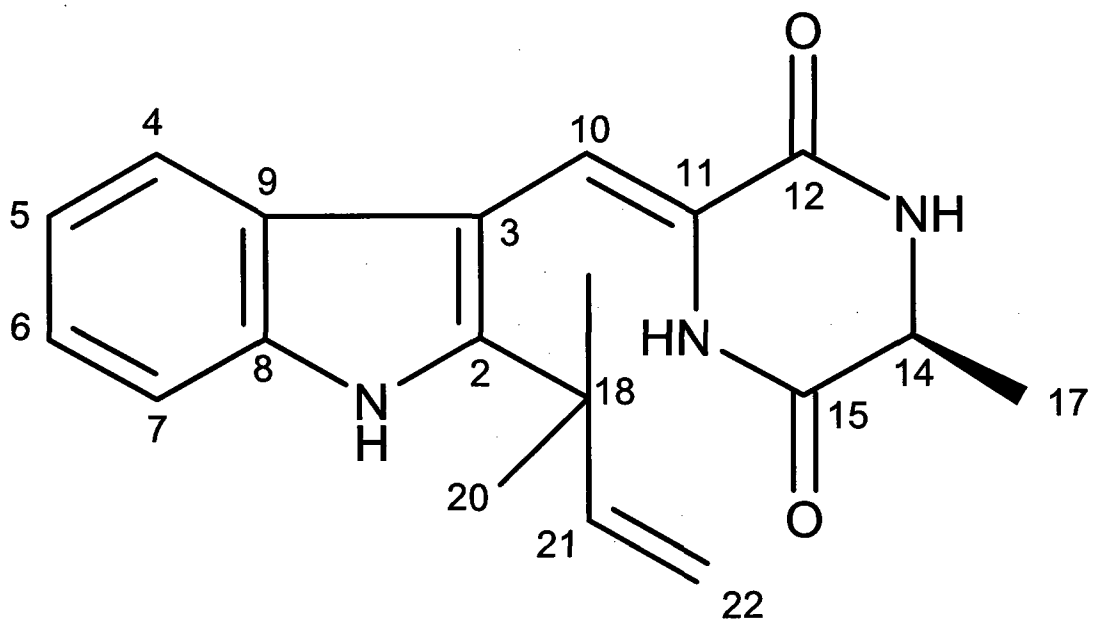


Figure 1 – Structure of Neoechinulin A (Slack et al., 2009)

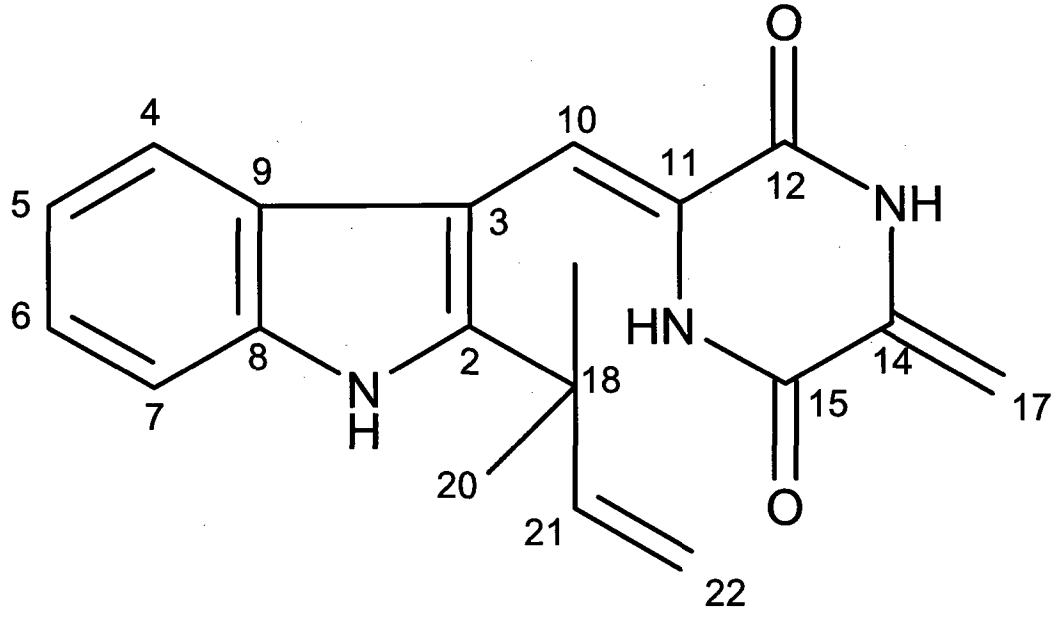


Figure 2 – Structure of Neoechinulin B (Slack et al., 2009)

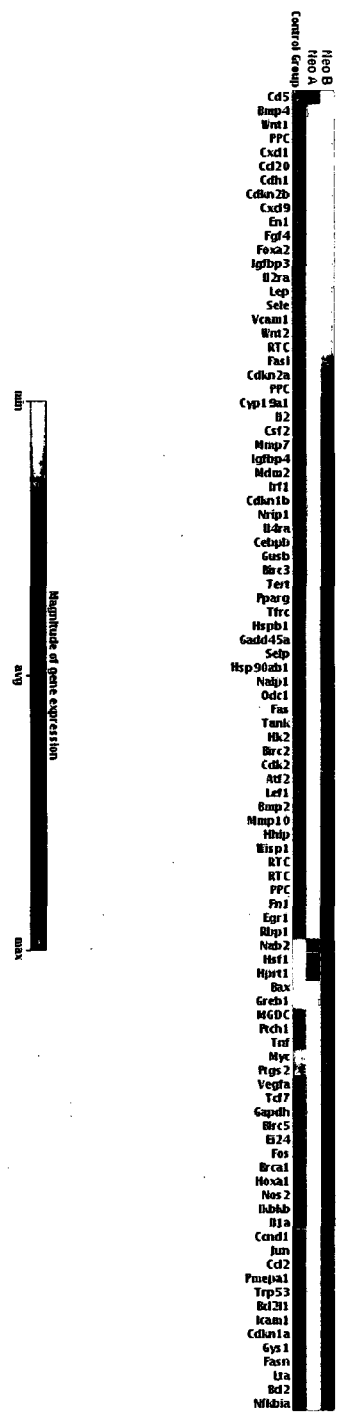


Figure 3 – Summary of results from Transduction Pathway Screening Experiment. Heat map showing levels of gene expression in RAW 264.7 cells exposed to $10^{-8}$M neoechinulin A and B at 2h PE. Green = lowest levels of gene expression; Red = highest levels of gene expression.

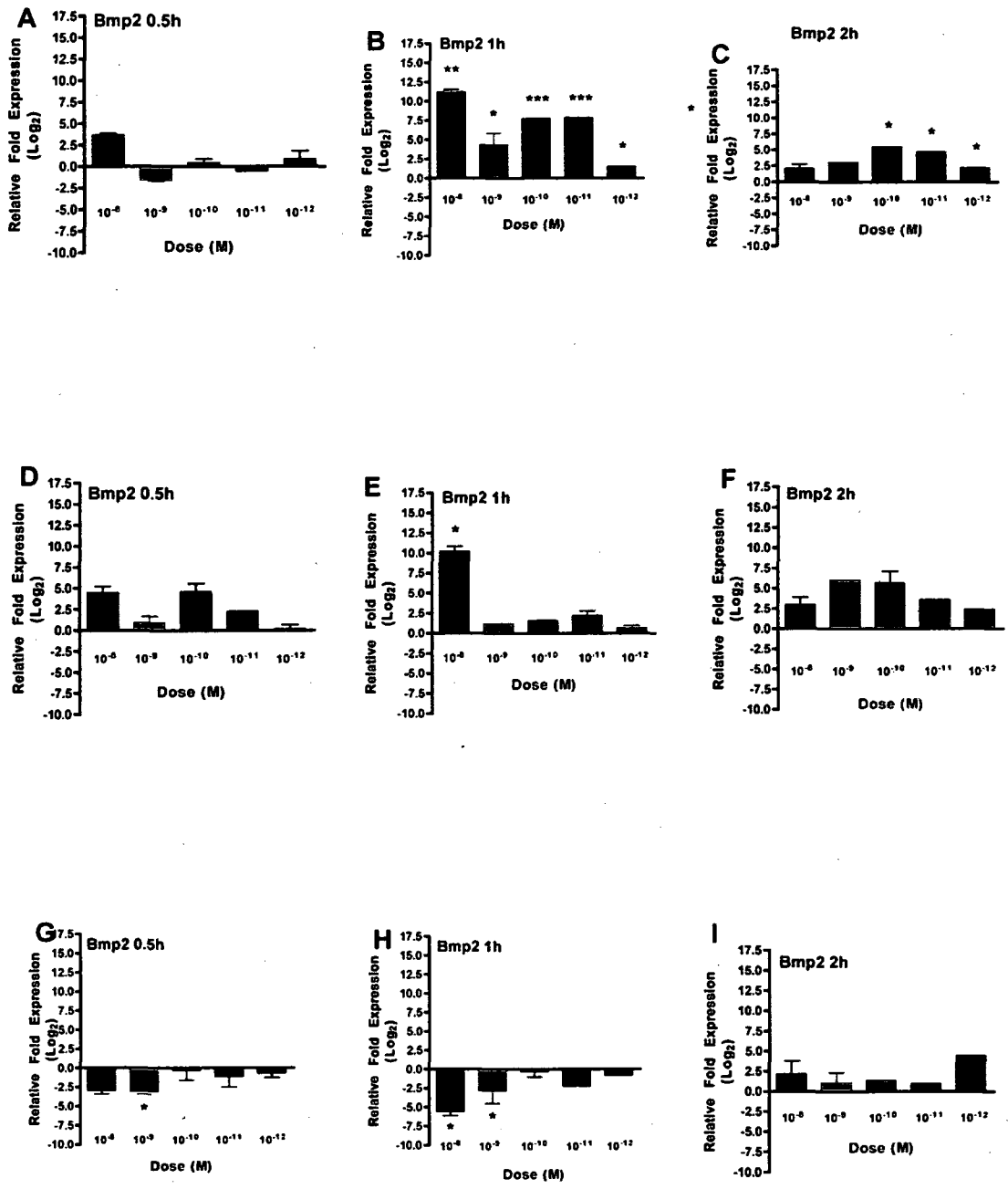


Figure 4 – Dose response of Bmp2 after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n = 3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls
** indicates significant difference from *
*** indicates significant difference from both * and **

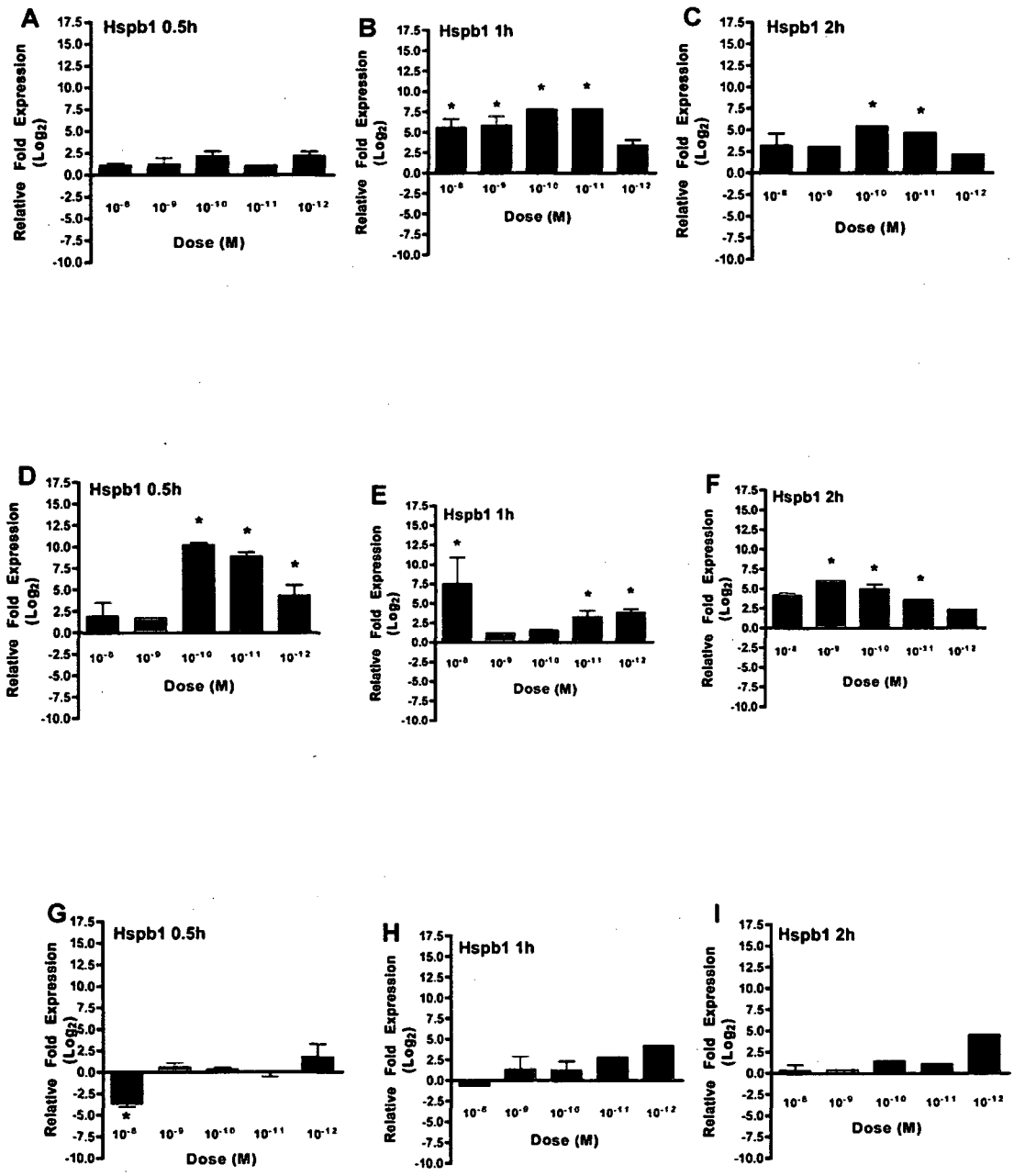


Figure 5 – Dose response of Hspb1 after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n = 3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls

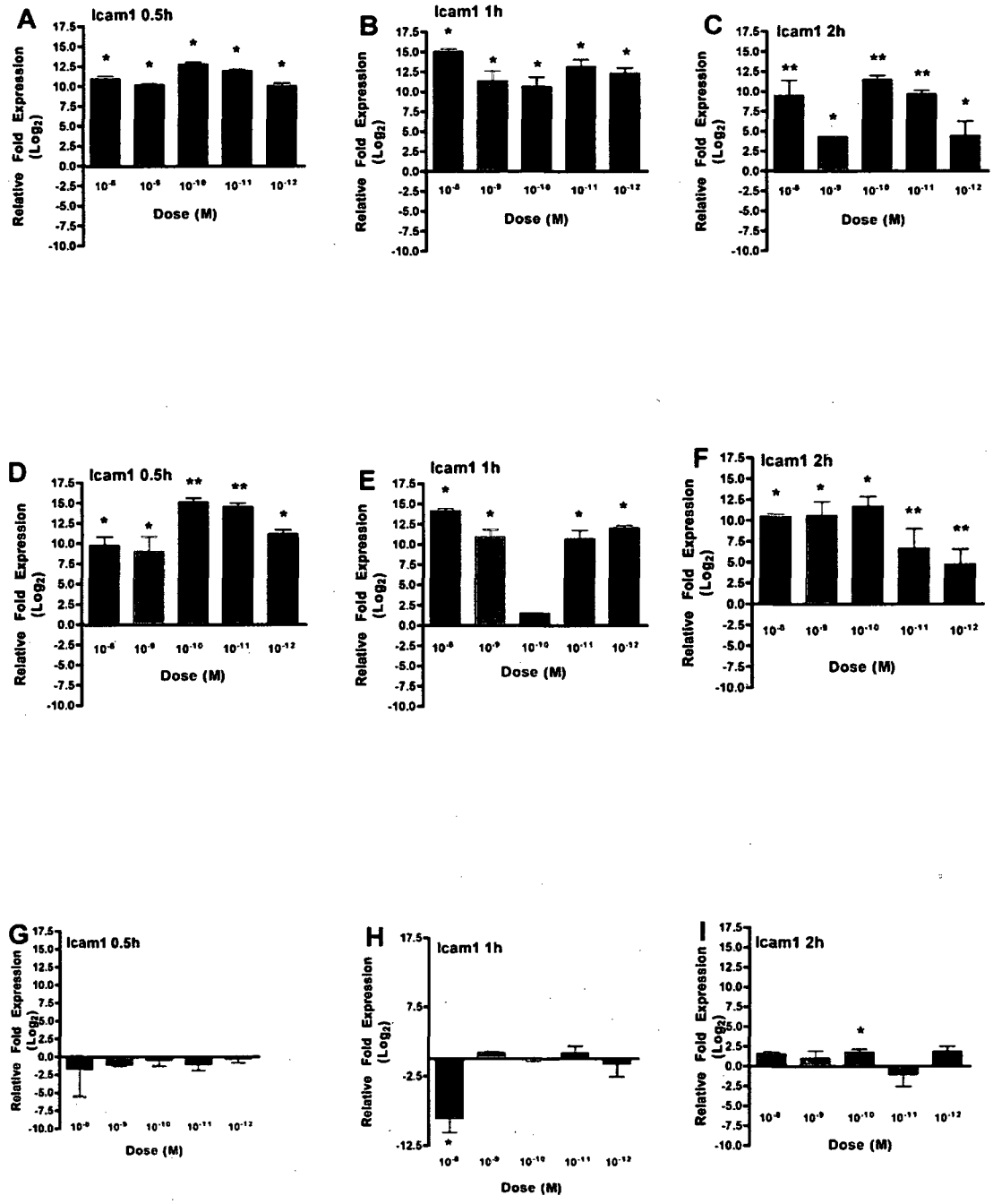


Figure 6 – Dose response of Icam1 after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n = 3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls
** indicates significant difference from *

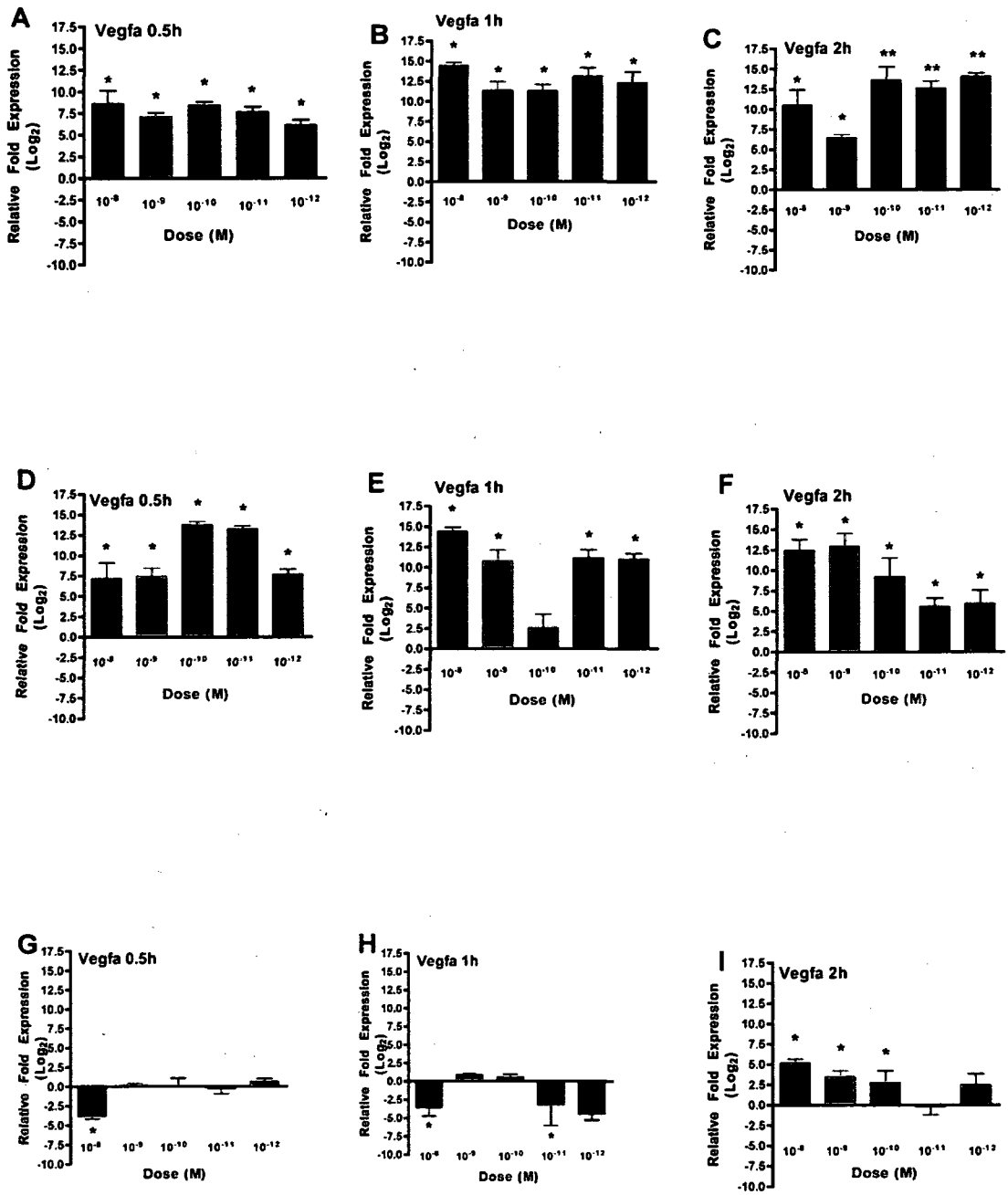


Figure 7 – Dose response of Vegfa after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n = 3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls
** indicates significant difference from *

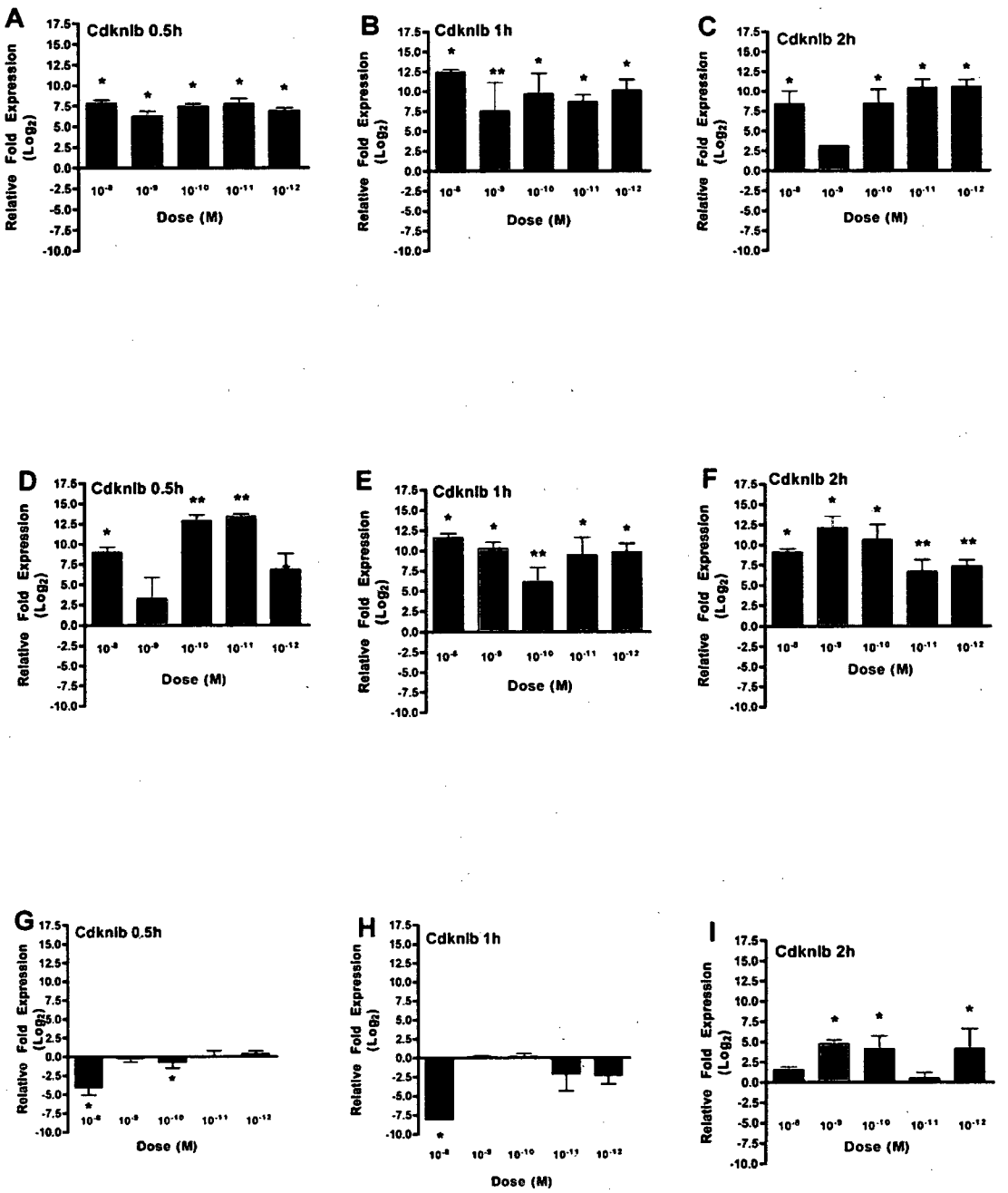


Figure 8 – Dose response of Cdknlb after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n=3 for each treatment)
* indicates significant regulation (P≤0.05) compared to controls
** indicates significant difference from *

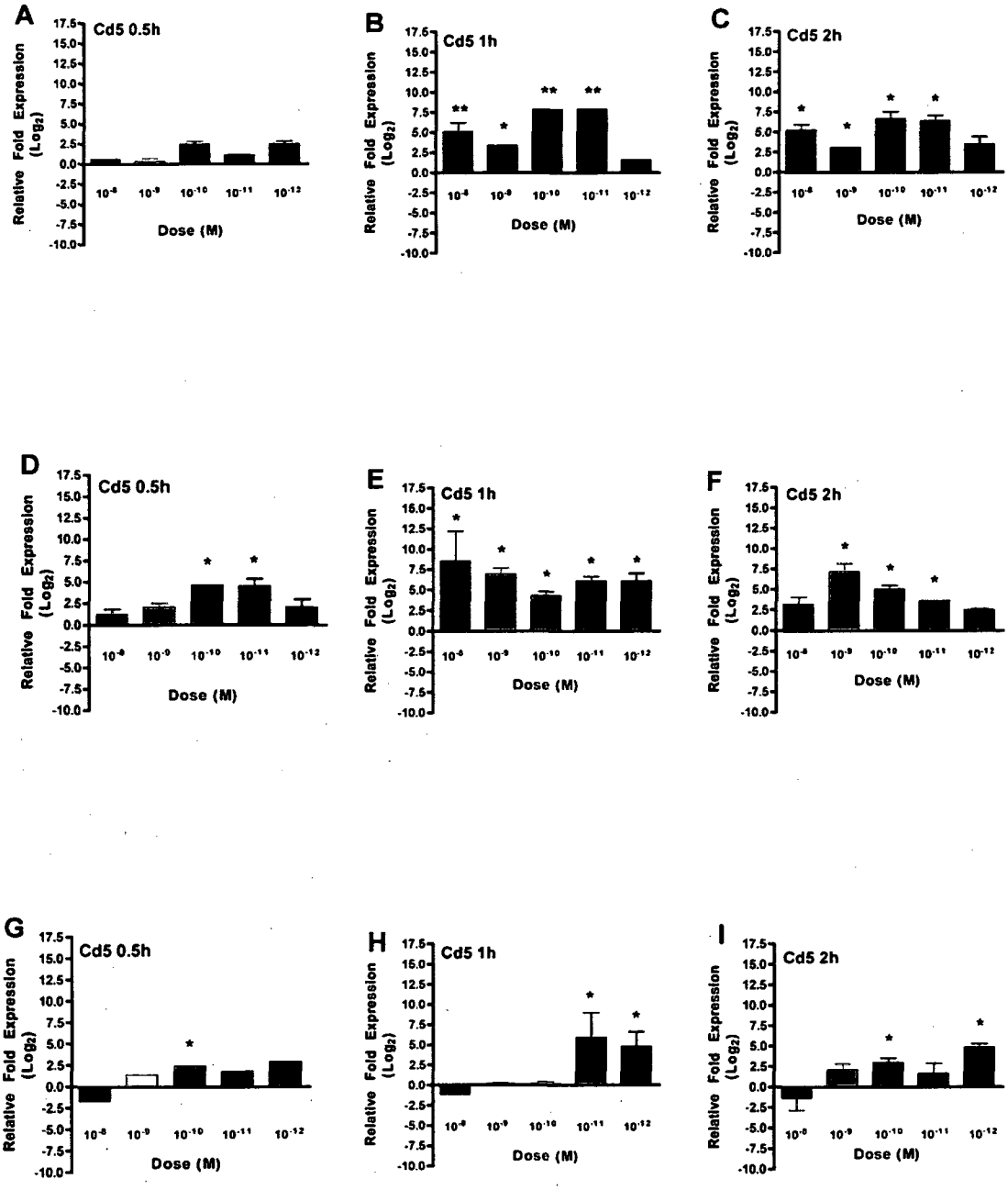


Figure 9 – Dose response of Cd5 after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n=3 for each treatment)
* indicates significant regulation (P≤0.05) compared to controls
** indicates significant difference from *

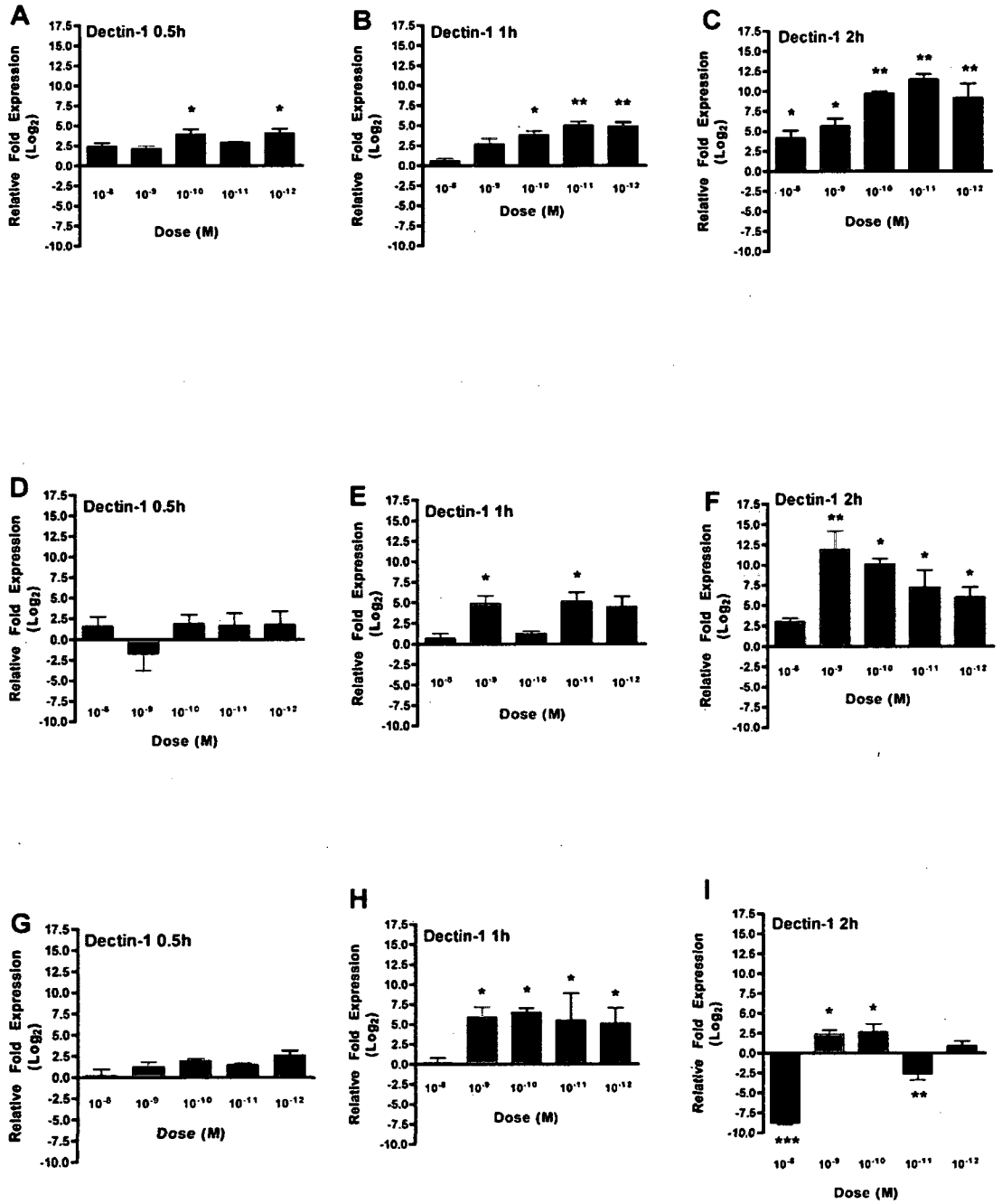


Figure 10 – Dose response of Dectin-1after exposure to neoechinulin A & B and β (1, 3) D glucan. The 1st column = 0.5h exposure (a,d,g); 2nd column = 1h (b,e,h); 3rd = 2h(c,f,i). The 1st row = neoechinulin A exposure (a,b,c); 2nd row = neoechinulin B (d,e,f); 3rd row = β (1, 3) D glucan. (n = 3 for each treatment)

* indicates significant regulation ($P \leq 0.05$) compared to controls

** indicates significant difference from *

*** indicates significant difference from both * and **

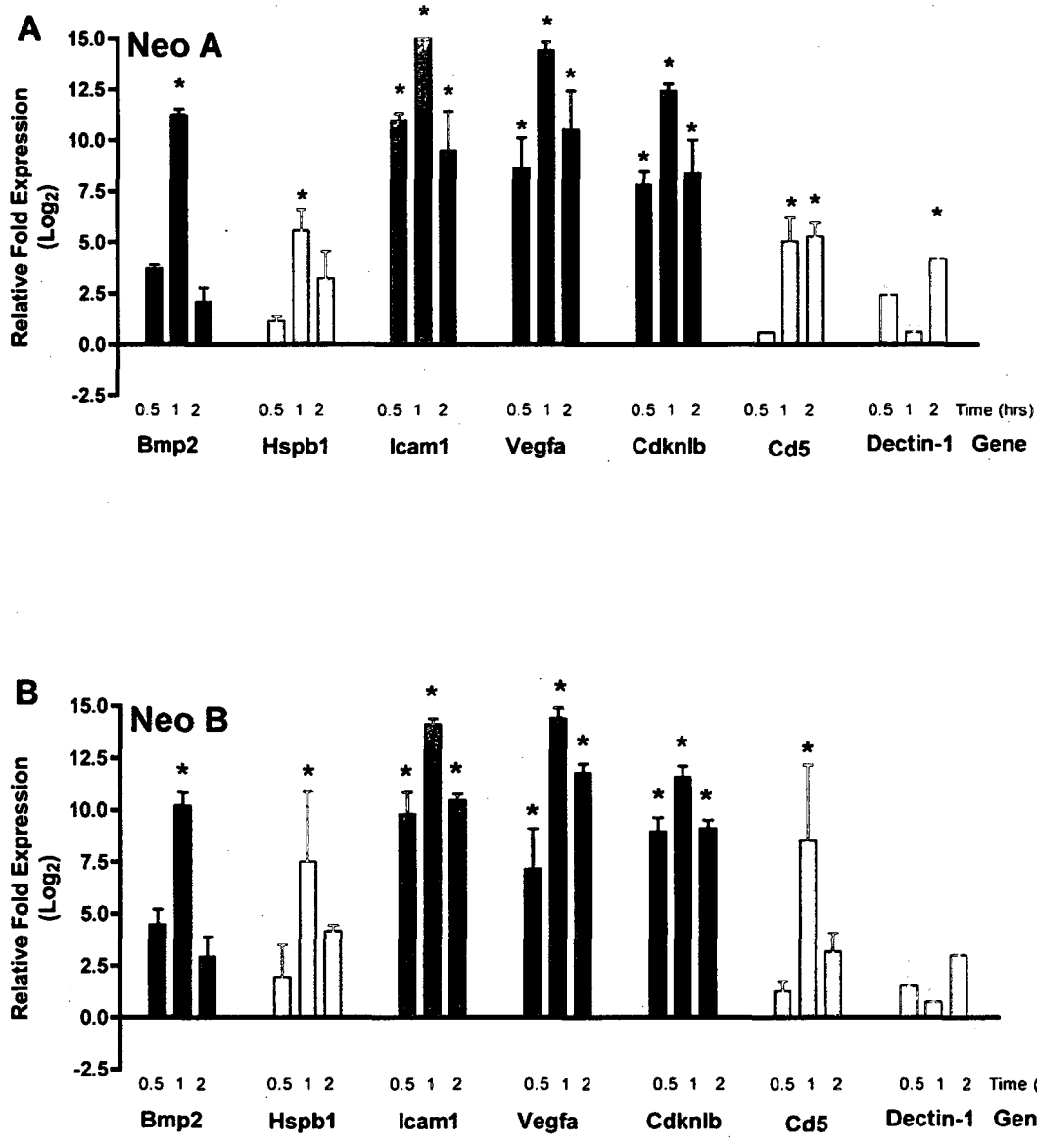


Figure 11 a-b - Temporal patterns of gene expression in RAW 264.7 murine macrophages. A = neoechinulin A $10^{-8}$M exposure; B = neoechinulin B $10^{-8}$M exposure (n=3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls

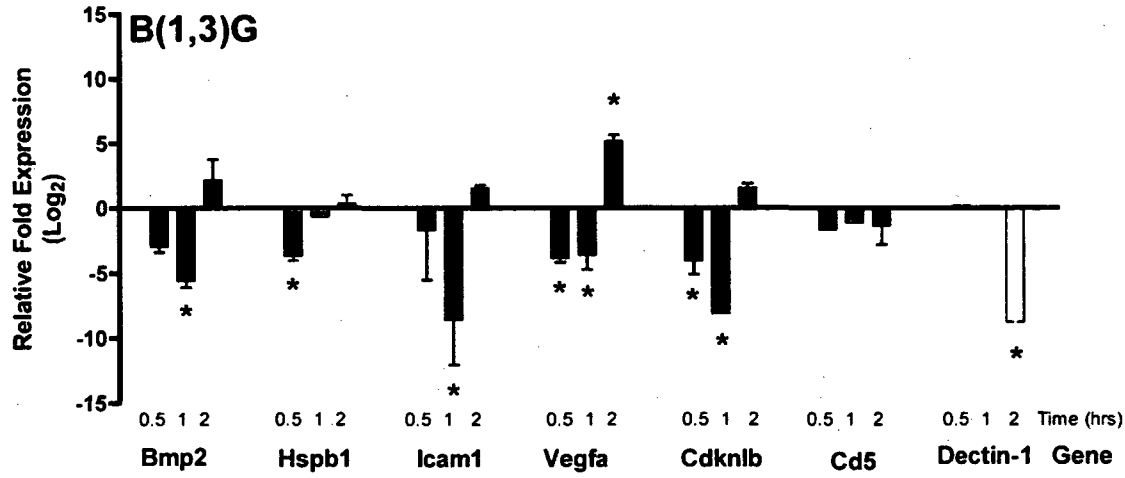


Figure 12 - Temporal patterns of gene expression in RAW 264.7 murine macrophages exposed to $10^{-8}$M β (1, 3) D-glucan (n=3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls

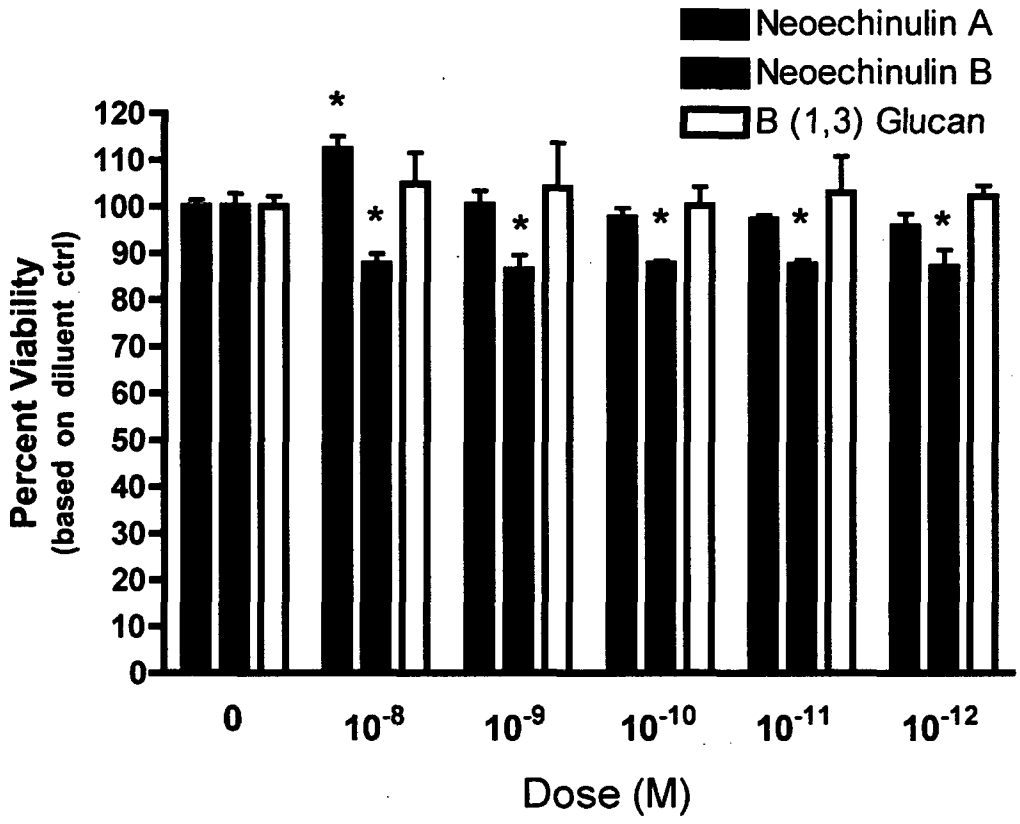


Figure 13 – Assessment of neoechinulin A & B and β (1, 3) D-glucan cytotoxicity by MTT (n=4 for each treatment)

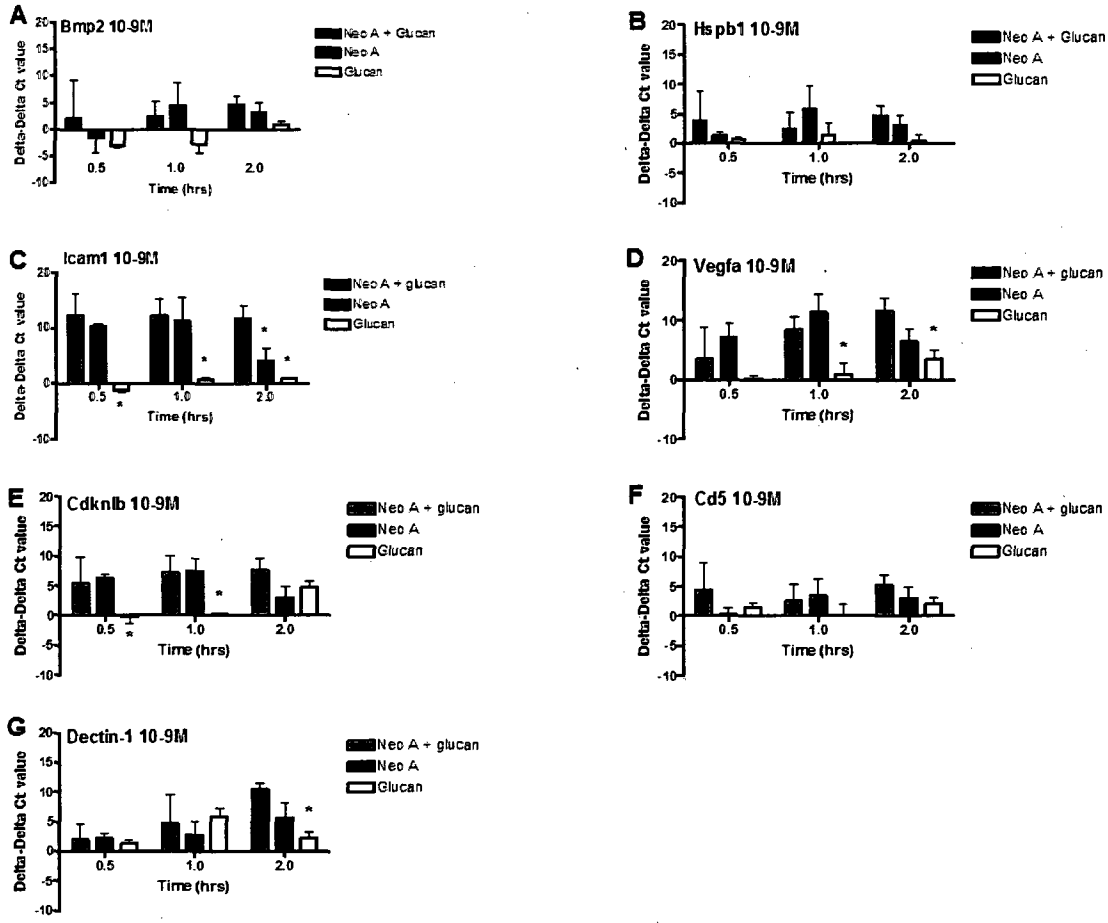


Figure 14 – Gene expression changes in AMs after exposure to neoechinulin A and β (1, 3) D-glucan simultaneously at concentrations of $10^{-9}$M for 30m, 1h and 2h exposures compared to neoechinulin A and β (1, 3) D-glucan alone. a = Bmp2, b = Hspb1, c = Icam1, d = Vegfa, e = Cdknlb, f = Cd5, g = Dectin-1. (n=3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls

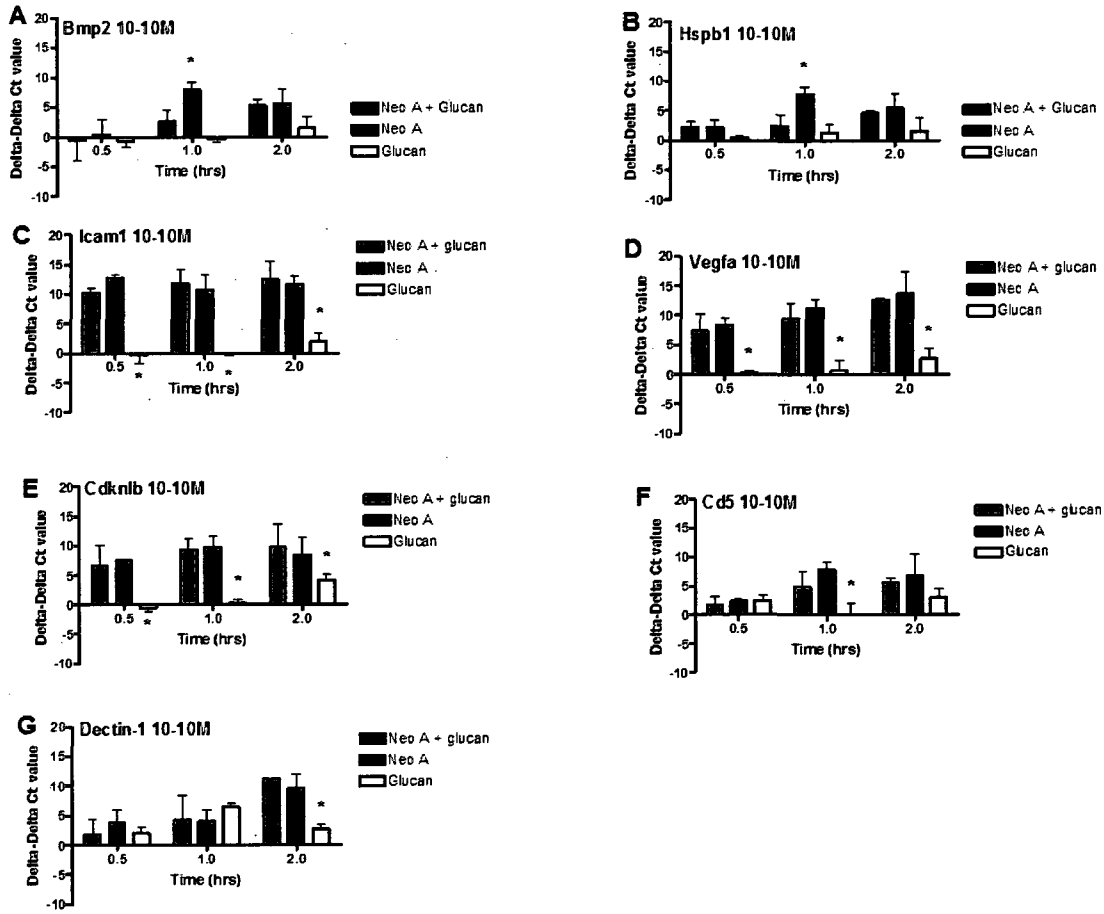


Figure 15 – Gene expression changes in AMs after simultaneous exposure to neoechinulin A and β (1, 3) D-glucan simultaneously at concentrations of $10^{-10}$M for 30m, 1h and 2h exposures compared to neoechinulin A and β (1, 3) D-glucan alone. a = Bmp2, b = Hspb1, c = Icam1, d = Vegfa, e = Cdknlb, f = Cd5, g = Dectin-1. (n=3 for each treatment)
* indicates significant regulation ($P \leq 0.05$) compared to controls

# APPENDIX I – ANOVA TABLES NEO A

| | |
|---|---|
| Table Analyzed | 10-8M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 18.39 | 0.0028 |
| Time | 34.83 | 0.0003 |
| Treatment | 36.47 | 0.0054 |
| Subjects (matching) | 4.8499 | 0.227 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 73.45 | 36.72 | 13.46 |
| Time | 2 | 139.1 | 69.54 | 25.49 |
| Treatment | 1 | 145.6 | 145.6 | 30.08 |
| Subjects (matching) | 4 | 19.37 | 4.842 | 1.775 |
| Residual | 8 | 21.82 | 2.728 | |

| | |
|---|---|
| Number of missing values | 0 |
| Bonferroni posttests | |

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 11.7 | -3.633 | -8.403 to 1.136 |
| 1 | 17.27 | 5.933 | -11.33 | -16.10 to -6.564 |
| 2 | 19.27 | 17.17 | -2.1 | -6.869 to 2.669 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.633 | 2.402 | P > 0.05 | ns |
| 1 | -11.33 | 7.492 | P<0.001 | *** |
| 2 | -2.1 | 1.388 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 12.97 | 0.1034 |
| Time | 25.93 | 0.0245 |
| Treatment | 40.86 | 0.0021 |
| Subjects (matching) | 3.2542 | 0.815 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 15.65 | 7.827 | 3.054 |
| Time | 2 | 31.31 | 15.65 | 6.108 |
| Treatment | 1 | 49.34 | 49.34 | 50.23 |
| Subjects (matching) | 4 | 3.929 | 0.9822 | 0.3832 |
| Residual | 8 | 20.5 | 2.563 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 15.9 | -1.067 | -4.740 to 2.606 |
| 1 | 17.27 | 11.63 | -5.633 | -9.306 to -1.960 |
| 2 | 19.27 | 16.03 | -3.233 | -6.906 to 0.4398 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.067 | 0.9155 | P > 0.05 | ns |
| 1 | -5.633 | 4.835 | P<0.01 | ** |
| 2 | -3.233 | 2.775 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 3.67 | 0.0058 |
| Time | 2.95 | 0.0107 |
| Treatment | 90.35 | 0.0001 |
| Subjects (matching) | 1.6265 | 0.1444 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 25.81 | 12.9 | 10.49 |
| Time | 2 | 20.73 | 10.37 | 8.425 |
| Treatment | 1 | 634.9 | 634.9 | 222.2 |
| Subjects (matching) | 4 | 11.43 | 2.857 | 2.322 |
| Residual | 8 | 9.844 | 1.231 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 6.033 | -10.93 | -14.36 to -7.506 |
| 1 | 17.17 | 2 | -15.17 | -18.59 to -11.74 |
| 2 | 16.87 | 7.333 | -9.533 | -12.96 to -6.106 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -10.93 | 10.06 | P<0.001 | *** |
| 1 | -15.17 | 13.95 | P<0.001 | *** |
| 2 | -9.533 | 8.769 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-8M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.08 | 0.0318 |
| Time | 7.13 | 0.0075 |
| Treatment | 84.01 | 0.0002 |
| Subjects (matching) | 1.7975 | 0.3795 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 27.4 | 13.7 | 5.471 |
| Time | 2 | 47.94 | 23.97 | 9.571 |
| Treatment | 1 | 564.5 | 564.5 | 186.9 |
| Subjects (matching) | 4 | 12.08 | 3.019 | 1.206 |
| Residual | 8 | 20.04 | 2.504 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 7.433 | -8.567 | -12.78 to -4.356 |
| 1 | 17.27 | 2.767 | -14.5 | -18.71 to -10.29 |
| 2 | 19.27 | 8.733 | -10.53 | -14.74 to -6.322 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -8.567 | 6.414 | P<0.001 | *** |
| 1 | -14.5 | 10.86 | P<0.001 | *** |
| 2 | -10.53 | 7.886 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-8M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.07 | 0.035 |
| Time | 10.1 | 0.0031 |
| Treatment | 82.08 | P<0.0001 |
| Subjects (matching) | 0.6439 | 0.7937 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 20.34 | 10.17 | 5.25 |
| Time | 2 | 50.43 | 25.22 | 13.02 |
| Treatment | 1 | 409.9 | 409.9 | 509.9 |
| Subjects (matching) | 4 | 3.216 | 0.8039 | 0.415 |
| Residual | 8 | 15.5 | 1.937 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 9.2 | -7.767 | -10.98 to -4.552 |
| 1 | 17.27 | 4.733 | -12.53 | -15.75 to -9.319 |
| 2 | 19.27 | 10.93 | -8.333 | -11.55 to -5.119 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.767 | 7.617 | P<0.001 | *** |
| 1 | -12.53 | 12.29 | P<0.001 | *** |
| 2 | -8.333 | 8.173 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-8M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 17.4 | 0.05 |
| Time | 12.36 | 0.0969 |
| Treatment | 47.72 | 0.0063 |
| Subjects (matching) | 6.906 | 0.5143 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 21.79 | 10.9 | 4.46 |
| Time | 2 | 15.48 | 7.742 | 3.169 |
| Treatment | 1 | 59.77 | 59.77 | 27.64 |
| Subjects (matching) | 4 | 8.649 | 2.162 | 0.885 |
| Residual | 8 | 19.54 | 2.443 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 16.43 | -0.5333 | -4.479 to 3.412 |
| 1 | 17.27 | 12.13 | -5.133 | -9.079 to -1.188 |
| 2 | 19.27 | 14 | -5.267 | -9.212 to -1.321 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5333 | 0.4261 | P > 0.05 | ns |
| 1 | -5.133 | 4.102 | P<0.01 | ** |
| 2 | -5.267 | 4.208 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-8M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.43 | 0.1716 |
| Time | 72.84 | 0.0002 |
| Treatment | 10.15 | 0.0088 |
| Subjects (matching) | 1.7828 | 0.828 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 12.25 | 6.124 | 2.215 |
| Time | 2 | 164.3 | 82.17 | 29.72 |
| Treatment | 1 | 22.89 | 22.89 | 22.77 |
| Subjects (matching) | 4 | 4.022 | 1.006 | 0.3637 |
| Residual | 8 | 22.12 | 2.765 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 8.7 | -2.4 | -6.199 to 1.399 |
| 1 | 12.4 | 12.23 | -0.1667 | -3.966 to 3.633 |
| 2 | 19.27 | 15.07 | -4.2 | -7.999 to -0.4008 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.4 | 1.992 | P > 0.05 | ns |
| 1 | -0.1667 | 0.1383 | P > 0.05 | ns |
| 2 | -4.2 | 3.485 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-9M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 25.62 | 0.0567 |
| Time | 19.29 | 0.0973 |
| Treatment | 15.64 | 0.1111 |
| Subjects (matching) | 15.0542 | 0.3696 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 29.81 | 14.9 | 4.199 |
| Time | 2 | 22.44 | 11.22 | 3.162 |
| Treatment | 1 | 18.2 | 18.2 | 4.156 |
| Subjects (matching) | 4 | 17.52 | 4.379 | 1.234 |
| Residual | 8 | 28.4 | 3.549 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 16.87 | 1.533 | -3.502 to 6.568 |
| 1 | 17.27 | 12.77 | -4.5 | -9.535 to 0.5352 |
| 2 | 19.27 | 16.2 | -3.067 | -8.102 to 1.968 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.533 | 0.9601 | P > 0.05 | ns |
| 1 | -4.5 | 2.818 | P < 0.05 | * |
| 2 | -3.067 | 1.92 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 11.83 | 0.1214 |
| Time | 26.54 | 0.0234 |
| Treatment | 40.15 | 0.0038 |
| Subjects (matching) | 4.4241 | 0.7248 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 15.73 | 7.867 | 2.777 |
| Time | 2 | 35.29 | 17.64 | 6.228 |
| Treatment | 1 | 53.39 | 53.39 | 36.31 |
| Subjects (matching) | 4 | 5.882 | 1.471 | 0.5191 |
| Residual | 8 | 22.66 | 2.833 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 15.6 | -1.367 | -5.337 to 2.604 |
| 1 | 17.27 | 11.37 | -5.9 | -9.870 to -1.930 |
| 2 | 19.27 | 16.2 | -3.067 | -7.037 to 0.9036 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.367 | 1.085 | P > 0.05 | ns |
| 1 | -5.9 | 4.685 | P<0.01 | ** |
| 2 | -3.067 | 2.435 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 9.65 | 0.0094 |
| Time | 8.42 | 0.0135 |
| Treatment | 74.88 | 0.0005 |
| Subjects (matching) | 2.6999 | 0.3674 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 43.43 | 21.72 | 8.862 |
| Time | 2 | 37.89 | 18.94 | 7.73 |
| Treatment | 1 | 337.1 | 337.1 | 110.9 |
| Subjects (matching) | 4 | 12.16 | 3.039 | 1.24 |
| Residual | 8 | 19.6 | 2.451 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 6.633 | -10.33 | -14.52 to -6.146 |
| 1 | 17.17 | 5.833 | -11.33 | -15.52 to -7.146 |
| 2 | 16.87 | 12.57 | -4.3 | -8.488 to -0.1122 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -10.33 | 7.779 | P<0.001 | *** |
| 1 | -11.33 | 8.532 | P<0.001 | *** |
| 2 | -4.3 | 3.237 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-9M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.9 | 0.0565 |
| Time | 15.71 | 0.0027 |
| Treatment | 71.58 | 0.0007 |
| Subjects (matching) | 3.1414 | 0.3326 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 21.33 | 10.67 | 4.203 |
| Time | 2 | 68.42 | 34.21 | 13.48 |
| Treatment | 1 | 311.7 | 311.7 | 91.15 |
| Subjects (matching) | 4 | 13.68 | 3.419 | 1.347 |
| Residual | 8 | 20.3 | 2.538 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 8.8 | -7.2 | -11.53 to -2.868 |
| 1 | 17.27 | 5.9 | -11.37 | -15.70 to -7.035 |
| 2 | 19.27 | 12.87 | -6.4 | -10.73 to -2.068 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.2 | 5.24 | P<0.001 | *** |
| 1 | -11.37 | 8.273 | P<0.001 | *** |
| 2 | -6.4 | 4.658 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-9M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.94 | 0.1894 |
| Time | 24.65 | 0.0103 |
| Treatment | 52.74 | 0.003 |
| Subjects (matching) | 5.136 | 0.5113 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 16.22 | 8.111 | 2.063 |
| Time | 2 | 67.27 | 33.63 | 8.555 |
| Treatment | 1 | 143.9 | 143.9 | 41.08 |
| Subjects (matching) | 4 | 14.02 | 3.504 | 0.8913 |
| Residual | 8 | 31.45 | 3.931 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 10.63 | -6.333 | -11.34 to -1.323 |
| 1 | 17.27 | 9.7 | -7.567 | -12.58 to -2.556 |
| 2 | 19.27 | 16.2 | -3.067 | -8.077 to 1.944 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6.333 | 3.985 | P<0.01 | ** |
| 1 | -7.567 | 4.761 | P<0.01 | ** |
| 2 | -3.067 | 1.93 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 12.02 | 0.2156 |
| Time | 21.5 | 0.0879 |
| Treatment | 35.79 | 0.0059 |
| Subjects (matching) | 4.9888 | 0.8116 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 8.148 | 4.074 | 1.87 |
| Time | 2 | 14.57 | 7.287 | 3.346 |
| Treatment | 1 | 24.27 | 24.27 | 28.7 |
| Subjects (matching) | 4 | 3.382 | 0.8456 | 0.3882 |
| Residual | 8 | 17.42 | 2.178 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 16.53 | -0.4333 | -3.823 to 2.956 |
| 1 | 17.27 | 13.8 | -3.467 | -6.856 to -0.07710 |
| 2 | 19.27 | 16.2 | -3.067 | -6.456 to 0.3229 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4333 | 0.403 | P > 0.05 | ns |
| 1 | -3.467 | 3.224 | P < 0.05 | * |
| 2 | -3.067 | 2.852 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-9M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.19 | 0.2243 |
| Time | 60.46 | 0.0003 |
| Treatment | 23.6 | 0.0036 |
| Subjects (matching) | 2.5015 | 0.7105 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 10.03 | 5.016 | 1.813 |
| Time | 2 | 144.8 | 72.41 | 26.17 |
| Treatment | 1 | 56.53 | 56.53 | 37.75 |
| Subjects (matching) | 4 | 5.991 | 1.498 | 0.5413 |
| Residual | 8 | 22.14 | 2.767 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 8.867 | -2.233 | -6.174 to 1.708 |
| 1 | 12.4 | 9.633 | -2.767 | -6.708 to 1.174 |
| 2 | 19.27 | 13.63 | -5.633 | -9.574 to -1.692 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.233 | 1.787 | P > 0.05 | ns |
| 1 | -2.767 | 2.213 | P > 0.05 | ns |
| 2 | -5.633 | 4.507 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-10M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 20.26 | 0.0104 |
| Time | 14.3 | 0.0254 |
| Treatment | 44.59 | 0.0166 |
| Subjects (matching) | 11.3433 | 0.1373 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 43.26 | 21.63 | 8.524 |
| Time | 2 | 30.55 | 15.27 | 6.019 |
| Treatment | 1 | 95.22 | 95.22 | 15.72 |
| Subjects (matching) | 4 | 24.22 | 6.056 | 2.386 |
| Residual | 8 | 20.3 | 2.538 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 14.9 | -0.4333 | -5.392 to 4.525 |
| 1 | 17.27 | 9.4 | -7.867 | -12.83 to -2.908 |
| 2 | 19.27 | 13.77 | -5.5 | -10.46 to -0.5415 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4333 | 0.2755 | P > 0.05 | ns |
| 1 | -7.867 | 5.002 | P<0.001 | *** |
| 2 | -5.5 | 3.497 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-10M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 19.72 | 0.013 |
| Time | 14.17 | 0.0297 |
| Treatment | 44.67 | 0.0166 |
| Subjects (matching) | 11.379 | 0.1513 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 42.43 | 21.22 | 7.842 |
| Time | 2 | 30.5 | 15.25 | 5.637 |
| Treatment | 1 | 96.14 | 96.14 | 15.7 |
| Subjects (matching) | 4 | 24.49 | 6.122 | 2.263 |
| Residual | 8 | 21.64 | 2.706 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 14.83 | -0.5 | -5.547 to 4.547 |
| 1 | 17.27 | 9.4 | -7.867 | -12.91 to -2.819 |
| 2 | 19.27 | 13.77 | -5.5 | -10.55 to -0.4528 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5 | 0.3123 | P > 0.05 | ns |
| 1 | -7.867 | 4.914 | P<0.01 | ** |
| 2 | -5.5 | 3.436 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-10M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 0.51 | 0.3242 |
| Time | 0.71 | 0.2211 |
| Treatment | 95.05 | 0.0002 |
| Subjects (matching) | 2.1759 | 0.1009 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 3.258 | 1.629 | 1.301 |
| Time | 2 | 4.591 | 2.296 | 1.833 |
| Treatment | 1 | 611.3 | 611.3 | 174.7 |
| Subjects (matching) | 4 | 14 | 3.499 | 2.794 |
| Residual | 8 | 10.02 | 1.252 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 4.2 | -12.77 | -16.41 to -9.125 |
| 1 | 17.17 | 6.467 | -10.7 | -14.34 to -7.059 |
| 2 | 16.87 | 5.367 | -11.5 | -15.14 to -7.859 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -12.77 | 11.05 | P<0.001 | *** |
| 1 | -10.7 | 9.264 | P<0.001 | *** |
| 2 | -11.5 | 9.957 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 3.35 | 0.0601 |
| Time | 0.4 | 0.6345 |
| Treatment | 89.82 | 0.0004 |
| Subjects (matching) | 3.1564 | 0.2001 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 20.66 | 10.33 | 4.078 |
| Time | 2 | 2.441 | 1.221 | 0.4817 |
| Treatment | 1 | 554.4 | 554.4 | 113.8 |
| Subjects (matching) | 4 | 19.48 | 4.871 | 1.923 |
| Residual | 8 | 20.27 | 2.534 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 7.633 | -8.367 | -13.05 to -3.681 |
| 1 | 17.27 | 5.933 | -11.33 | -16.02 to -6.648 |
| 2 | 19.27 | 5.667 | -13.6 | -18.29 to -8.915 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -8.367 | 5.63 | P<0.001 | *** |
| 1 | -11.33 | 7.626 | P<0.001 | *** |
| 2 | -13.6 | 9.151 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 1.06 | 0.6159 |
| Time | 5.51 | 0.1293 |
| Treatment | 82.91 | 0.0003 |
| Subjects (matching) | 2.2534 | 0.7076 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 4.214 | 2.107 | 0.5152 |
| Time | 2 | 21.85 | 10.92 | 2.671 |
| Treatment | 1 | 328.5 | 328.5 | 147.2 |
| Subjects (matching) | 4 | 8.929 | 2.232 | 0.5458 |
| Residual | 8 | 32.72 | 4.09 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 9.567 | -7.4 | -12.20 to -2.605 |
| 1 | 17.27 | 7.5 | -9.767 | -14.56 to -4.971 |
| 2 | 19.27 | 10.8 | -8.467 | -13.26 to -3.671 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.4 | 4.865 | P<0.01 | ** |
| 1 | -9.767 | 6.421 | P<0.001 | *** |
| 2 | -8.467 | 5.566 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 10.87 | 0.0276 |
| Time | 11.24 | 0.0255 |
| Treatment | 64.03 | 0.0032 |
| Subjects (matching) | 6.3803 | 0.2408 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 24.44 | 12.22 | 5.818 |
| Time | 2 | 25.27 | 12.63 | 6.015 |
| Treatment | 1 | 143.9 | 143.9 | 40.14 |
| Subjects (matching) | 4 | 14.34 | 3.586 | 1.707 |
| Residual | 8 | 16.8 | 2.101 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 14.53 | -2.433 | -6.580 to 1.714 |
| 1 | 17.27 | 9.4 | -7.867 | -12.01 to -3.720 |
| 2 | 19.27 | 12.6 | -6.667 | -10.81 to -2.520 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.433 | 1.85 | P > 0.05 | ns |
| 1 | -7.867 | 5.98 | P<0.001 | *** |
| 2 | -6.667 | 5.068 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 10.85 | 0.0289 |
| Time | 28.82 | 0.0019 |
| Treatment | 49.47 | 0.0015 |
| Subjects (matching) | 3.2601 | 0.5283 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 33.83 | 16.92 | 5.703 |
| Time | 2 | 89.89 | 44.94 | 15.15 |
| Treatment | 1 | 154.3 | 154.3 | 60.69 |
| Subjects (matching) | 4 | 10.17 | 2.542 | 0.857 |
| Residual | 8 | 23.73 | 2.966 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 7.2 | -3.9 | -8.227 to 0.4266 |
| 1 | 12.4 | 8.467 | -3.933 | -8.260 to 0.3932 |
| 2 | 19.27 | 9.533 | -9.733 | -14.06 to -5.407 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.9 | 2.842 | P < 0.05 | * |
| 1 | -3.933 | 2.866 | P < 0.05 | * |
| 2 | -9.733 | 7.092 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 25.64 | 0.0076 |
| Time | 19 | 0.0171 |
| Treatment | 34.13 | 0.0225 |
| Subjects (matching) | 10.4584 | 0.1967 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 54.7 | 27.35 | 9.527 |
| Time | 2 | 40.54 | 20.27 | 7.061 |
| Treatment | 1 | 72.8 | 72.8 | 13.05 |
| Subjects (matching) | 4 | 22.31 | 5.577 | 1.943 |
| Residual | 8 | 22.96 | 2.871 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 15.87 | 0.5333 | -4.467 to 5.533 |
| 1 | 17.27 | 9.333 | -7.933 | -12.93 to -2.933 |
| 2 | 19.27 | 14.6 | -4.667 | -9.667 to 0.3333 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.5333 | 0.3363 | P > 0.05 | ns |
| 1 | -7.933 | 5.002 | P<0.001 | *** |
| 2 | -4.667 | 2.943 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-11M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 25.64 | 0.0076 |
| Time | 19 | 0.0171 |
| Treatment | 34.13 | 0.0225 |
| Subjects (matching) | 10.4584 | 0.1967 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 54.7 | 27.35 | 9.527 |
| Time | 2 | 40.54 | 20.27 | 7.061 |
| Treatment | 1 | 72.8 | 72.8 | 13.05 |
| Subjects (matching) | 4 | 22.31 | 5.577 | 1.943 |
| Residual | 8 | 22.96 | 2.871 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 15.87 | 0.5333 | -4.467 to 5.533 |
| 1 | 17.27 | 9.333 | -7.933 | -12.93 to -2.933 |
| 2 | 19.27 | 14.6 | -4.667 | -9.667 to 0.3333 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.5333 | 0.3363 | P > 0.05 | ns |
| 1 | -7.933 | 5.002 | P<0.001 | *** |
| 2 | -4.667 | 2.943 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-11M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 1.47 | 0.1016 |
| Time | 1.04 | 0.1742 |
| Treatment | 92.84 | 0.0003 |
| Subjects (matching) | 2.7492 | 0.0942 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 9.648 | 4.824 | 3.085 |
| Time | 2 | 6.854 | 3.427 | 2.191 |
| Treatment | 1 | 610.2 | 610.2 | 135.1 |
| Subjects (matching) | 4 | 18.07 | 4.517 | 2.888 |
| Residual | 8 | 12.51 | 1.564 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 4.967 | -12 | -16.11 to -7.891 |
| 1 | 17.17 | 3.933 | -13.23 | -17.34 to -9.124 |
| 2 | 16.87 | 7.167 | -9.7 | -13.81 to -5.591 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -12 | 9.207 | P<0.001 | *** |
| 1 | -13.23 | 10.15 | P<0.001 | *** |
| 2 | -9.7 | 7.442 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.67 | 0.0481 |
| Time | 2.16 | 0.0738 |
| Treatment | 88.87 | 0.0007 |
| Subjects (matching) | 3.9584 | 0.0674 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 15.16 | 7.582 | 4.542 |
| Time | 2 | 12.26 | 6.132 | 3.673 |
| Treatment | 1 | 505.6 | 505.6 | 89.81 |
| Subjects (matching) | 4 | 22.52 | 5.63 | 3.373 |
| Residual | 8 | 13.35 | 1.669 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 8.367 | -8.6 | -13.05 to -4.149 |
| 1 | 17.17 | 4.133 | -13.03 | -17.48 to -8.583 |
| 2 | 16.87 | 6.7 | -10.17 | -14.62 to -5.716 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -8.6 | 6.092 | P<0.001 | *** |
| 1 | -13.03 | 9.232 | P<0.001 | *** |
| 2 | -10.17 | 7.202 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 1.41 | 0.41 |
| Time | 1.11 | 0.4863 |
| Treatment | 90.44 | P<0.0001 |
| Subjects (matching) | 1.4022 | 0.7388 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 5.614 | 2.807 | 0.9988 |
| Time | 2 | 4.441 | 2.221 | 0.7901 |
| Treatment | 1 | 360.9 | 360.9 | 258 |
| Subjects (matching) | 4 | 5.596 | 1.399 | 0.4977 |
| Residual | 8 | 22.48 | 2.811 | |

| | |
|---|---|
| Number of missing values | 0 |

*Bonferroni posttests*

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 9.233 | -7.733 | -11.67 to -3.796 |
| 1 | 17.27 | 8.567 | -8.7 | -12.64 to -4.762 |
| 2 | 19.27 | 8.833 | -10.43 | -14.37 to -6.496 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.733 | 6.192 | P<0.001 | *** |
| 1 | -8.7 | 6.966 | P<0.001 | *** |
| 2 | -10.43 | 8.353 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 17.42 | 0.0155 |
| Time | 16.12 | 0.0189 |
| Treatment | 54.47 | 0.0007 |
| Subjects (matching) | 2.493 | 0.721 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 37.92 | 18.96 | 7.337 |
| Time | 2 | 35.08 | 17.54 | 6.787 |
| Treatment | 1 | 118.6 | 118.6 | 87.41 |
| Subjects (matching) | 4 | 5.427 | 1.357 | 0.525 |
| Residual | 8 | 20.67 | 2.584 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 15.83 | -1.133 | -4.930 to 2.663 |
| 1 | 17.27 | 9.333 | -7.933 | -11.73 to -4.137 |
| 2 | 19.27 | 12.93 | -6.333 | -10.13 to -2.537 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.133 | 0.9412 | P > 0.05 | ns |
| 1 | -7.933 | 6.588 | P<0.001 | *** |
| 2 | -6.333 | 5.26 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 17.5 | 0.0075 |
| Time | 16.41 | 0.009 |
| Treatment | 55.49 | 0.0012 |
| Subjects (matching) | 3.2863 | 0.5074 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 60.16 | 30.08 | 9.577 |
| Time | 2 | 56.41 | 28.21 | 8.98 |
| Treatment | 1 | 190.8 | 190.8 | 67.54 |
| Subjects (matching) | 4 | 11.3 | 2.824 | 0.8992 |
| Residual | 8 | 25.13 | 3.141 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 8.167 | -2.933 | -7.418 to 1.552 |
| 1 | 12.4 | 7.333 | -5.067 | -9.552 to -0.5818 |
| 2 | 19.27 | 7.733 | -11.53 | -16.02 to -7.048 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.933 | 2.062 | P > 0.05 | ns |
| 1 | -5.067 | 3.562 | P < 0.05 | * |
| 2 | -11.53 | 8.107 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-12M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 1.26 | 0.8483 |
| Time | 35.22 | 0.0452 |
| Treatment | 12.09 | 0.2062 |
| Subjects (matching) | 21.2949 | 0.313 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 1.188 | 0.5939 | 0.1679 |
| Time | 2 | 33.08 | 16.54 | 4.676 |
| Treatment | 1 | 11.36 | 11.36 | 2.272 |
| Subjects (matching) | 4 | 20 | 5.001 | 1.414 |
| Residual | 8 | 28.3 | 3.537 | |

| | |
|---|---|
| Number of missing values | 0 |

*Bonferroni posttests*

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 14.43 | -0.9 | -6.064 to 4.264 |
| 1 | 17.27 | 15.53 | -1.733 | -6.898 to 3.431 |
| 2 | 19.27 | 17.13 | -2.133 | -7.298 to 3.031 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9 | 0.5494 | P > 0.05 | ns |
| 1 | -1.733 | 1.058 | P > 0.05 | ns |
| 2 | -2.133 | 1.302 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.86 | 0.4274 |
| Time | 31.81 | 0.0366 |
| Treatment | 17.81 | 0.1305 |
| Subjects (matching) | 19.7762 | 0.265 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.458 | 3.229 | 0.947 |
| Time | 2 | 35.07 | 17.54 | 5.143 |
| Treatment | 1 | 19.64 | 19.64 | 3.602 |
| Subjects (matching) | 4 | 21.8 | 5.451 | 1.599 |
| Residual | 8 | 27.28 | 3.41 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 14.73 | -0.6 | -5.806 to 4.606 |
| 1 | 17.27 | 13.73 | -3.533 | -8.739 to 1.673 |
| 2 | 19.27 | 17.13 | -2.133 | -7.339 to 3.073 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.6 | 0.3634 | P > 0.05 | ns |
| 1 | -3.533 | 2.14 | P > 0.05 | ns |
| 2 | -2.133 | 1.292 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 10.39 | 0.0111 |
| Time | 9.05 | 0.016 |
| Treatment | 73.25 | 0.0004 |
| Subjects (matching) | 2.3079 | 0.4956 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 51.58 | 25.79 | 8.32 |
| Time | 2 | 44.93 | 22.47 | 7.248 |
| Treatment | 1 | 363.6 | 363.6 | 127 |
| Subjects (matching) | 4 | 11.46 | 2.864 | 0.9239 |
| Residual | 8 | 24.8 | 3.1 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 6.867 | -10.1 | -14.57 to -5.626 |
| 1 | 17.17 | 4.7 | -12.47 | -16.94 to -7.992 |
| 2 | 16.87 | 12.47 | -4.4 | -8.874 to 0.07422 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -10.1 | 7.117 | P<0.001 | *** |
| 1 | -12.47 | 8.784 | P<0.001 | *** |
| 2 | -4.4 | 3.1 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-12M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 8.22 | 0.0134 |
| Time | 1.69 | 0.2621 |
| Treatment | 84.09 | 0.0002 |
| Subjects (matching) | 1.7544 | 0.5436 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 52.17 | 26.09 | 7.754 |
| Time | 2 | 10.7 | 5.352 | 1.591 |
| Treatment | 1 | 533.6 | 533.6 | 191.7 |
| Subjects (matching) | 4 | 11.13 | 2.783 | 0.8271 |
| Residual | 8 | 26.92 | 3.364 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 9.833 | -6.167 | -10.75 to -1.583 |
| 1 | 17.27 | 4.833 | -12.43 | -17.02 to -7.850 |
| 2 | 19.27 | 5.2 | -14.07 | -18.65 to -9.483 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6.167 | 4.242 | P<0.01 | ** |
| 1 | -12.43 | 8.552 | P<0.001 | *** |
| 2 | -14.07 | 9.675 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-12M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.73 | 0.2193 |
| Time | 2.51 | 0.2435 |
| Treatment | 87.54 | P<0.0001 |
| Subjects (matching) | 1.2991 | 0.7778 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 11.97 | 5.985 | 1.845 |
| Time | 2 | 10.99 | 5.495 | 1.694 |
| Treatment | 1 | 383.6 | 383.6 | 269.5 |
| Subjects (matching) | 4 | 5.693 | 1.423 | 0.4388 |
| Residual | 8 | 25.95 | 3.243 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 10.03 | -6.933 | -11.11 to -2.753 |
| 1 | 17.27 | 7.033 | -10.23 | -14.41 to -6.053 |
| 2 | 19.27 | 8.733 | -10.53 | -14.71 to -6.353 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6.933 | 5.23 | P<0.001 | *** |
| 1 | -10.23 | 7.719 | P<0.001 | *** |
| 2 | -10.53 | 7.945 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-12M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 3.05 | 0.7275 |
| Time | 13.9 | 0.2784 |
| Treatment | 40.46 | 0.0059 |
| Subjects (matching) | 5.686 | 0.8647 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 2.258 | 1.129 | 0.3312 |
| Time | 2 | 10.27 | 5.136 | 1.507 |
| Treatment | 1 | 29.9 | 29.9 | 28.46 |
| Subjects (matching) | 4 | 4.202 | 1.051 | 0.3082 |
| Residual | 8 | 27.27 | 3.409 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 14.43 | -2.533 | -6.702 to 1.636 |
| 1 | 17.27 | 15.53 | -1.733 | -5.902 to 2.436 |
| 2 | 19.27 | 15.8 | -3.467 | -7.636 to 0.7022 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.533 | 1.916 | P > 0.05 | ns |
| 1 | -1.733 | 1.311 | P > 0.05 | ns |
| 2 | -3.467 | 2.622 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 6.44 | 0.1262 |
| Time | 33.22 | 0.0024 |
| Treatment | 49.72 | 0.0002 |
| Subjects (matching) | 1.1232 | 0.91 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 21.6 | 10.8 | 2.711 |
| Time | 2 | 111.5 | 55.74 | 13.99 |
| Treatment | 1 | 166.8 | 166.8 | 177.1 |
| *Subjects (matching)* | 4 | 3.769 | 0.9422 | 0.2365 |
| Residual | 8 | 31.88 | 3.985 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo A

| Treatment | Saline | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 7.033 | -4.067 | -8.503 to 0.3700 |
| 1 | 12.4 | 7.333 | -5.067 | -9.503 to -0.6300 |
| 2 | 19.27 | 10.13 | -9.133 | -13.57 to -4.697 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.067 | 2.89 | P < 0.05 | * |
| 1 | -5.067 | 3.6 | P < 0.05 | * |
| 2 | -9.133 | 6.49 | P<0.001 | *** |

## APPENDIX II – ANOVA TABLES NEO B

| | |
|---|---|
| Table Analyzed | 10-8M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 21.35 | 0.0006 |
| Time | 23.36 | 0.0004 |
| Treatment | 39.41 | 0.0222 |
| Subjects (matching) | 11.9708 | 0.0148 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | *** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | * | Yes |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 67.05 | 33.52 | 21.8 |
| Time | 2 | 73.36 | 36.68 | 23.85 |
| Treatment | 1 | 123.8 | 123.8 | 13.17 |
| Subjects (matching) | 4 | 37.6 | 9.399 | 6.112 |
| Residual | 8 | 12.3 | 1.538 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 10.83 | -4.5 | -9.128 to 0.1278 |
| 1 | 17.27 | 6.967 | -10.3 | -14.93 to -5.672 |
| 2 | 17.27 | 16.33 | -0.9333 | -5.561 to 3.694 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.5 | 2.703 | P > 0.05 | ns |
| 1 | -10.3 | 6.186 | P<0.001 | *** |
| 2 | -0.9333 | 0.5606 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 11.39 | 0.1669 |
| Time | 20.4 | 0.0611 |
| Treatment | 44.76 | 0.0018 |
| Subjects (matching) | 3.2754 | 0.8539 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 23.88 | 11.94 | 2.259 |
| Time | 2 | 42.76 | 21.38 | 4.044 |
| Treatment | 1 | 93.85 | 93.85 | 54.67 |
| Subjects (matching) | 4 | 6.867 | 1.717 | 0.3247 |
| Residual | 8 | 42.29 | 5.287 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 15 | -1.967 | -7.177 to 3.243 |
| 1 | 17.27 | 9.7 | -7.567 | -12.78 to -2.357 |
| 2 | 19.27 | 15.1 | -4.167 | -9.377 to 1.043 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.967 | 1.19 | P > 0.05 | ns |
| 1 | -7.567 | 4.579 | P<0.01 | ** |
| 2 | -4.167 | 2.521 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.53 | 0.0318 |
| Time | 1.99 | 0.0542 |
| Treatment | 91.52 | 0.0002 |
| Subjects (matching) | 2.1152 | 0.1487 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 16.43 | 8.217 | 5.47 |
| Time | 2 | 12.89 | 6.444 | 4.29 |
| Treatment | 1 | 594 | 594 | 173.1 |
| Subjects (matching) | 4 | 13.73 | 3.432 | 2.285 |
| Residual | 8 | 12.02 | 1.502 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 7.133 | -9.833 | -13.60 to -6.063 |
| 1 | 17.17 | 3 | -14.17 | -17.94 to -10.40 |
| 2 | 16.87 | 6.4 | -10.47 | -14.24 to -6.696 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -9.833 | 8.222 | P<0.001 | *** |
| 1 | -14.17 | 11.85 | P<0.001 | *** |
| 2 | -10.47 | 8.752 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-8M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 6.2 | 0.01 |
| Time | 5.42 | 0.0143 |
| Treatment | 84.04 | 0.0001 |
| Subjects (matching) | 1.474 | 0.4482 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 41.2 | 20.6 | 8.654 |
| Time | 2 | 36.06 | 18.03 | 7.573 |
| Treatment | 1 | 558.9 | 558.9 | 228.1 |
| Subjects (matching) | 4 | 9.802 | 2.451 | 1.029 |
| Residual | 8 | 19.04 | 2.381 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 8.833 | -7.167 | -11.16 to -3.176 |
| 1 | 17.27 | 2.767 | -14.5 | -18.49 to -10.51 |
| 2 | 19.27 | 7.5 | -11.77 | -15.76 to -7.776 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.167 | 5.661 | P<0.001 | *** |
| 1 | -14.5 | 11.45 | P<0.001 | *** |
| 2 | -11.77 | 9.295 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-8M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 1.35 | 0.2774 |
| Time | 6.64 | 0.0148 |
| Treatment | 86.96 | 0.0001 |
| Subjects (matching) | 1.4948 | 0.5371 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.854 | 3.427 | 1.512 |
| Time | 2 | 33.82 | 16.91 | 7.459 |
| Treatment | 1 | 443 | 443 | 232.7 |
| Subjects (matching) | 4 | 7.616 | 1.904 | 0.8397 |
| Residual | 8 | 18.14 | 2.267 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 7.967 | -9 | -12.77 to -5.229 |
| 1 | 17.27 | 5.6 | -11.67 | -15.44 to -7.896 |
| 2 | 19.27 | 10.17 | -9.1 | -12.87 to -5.329 |

| *Treatment* | *Difference* | t | *P value* | *Summary* |
|---|---|---|---|---|
| 0.5 | -9 | 7.524 | P<0.001 | *** |
| 1 | -11.67 | 9.754 | P<0.001 | *** |
| 2 | -9.1 | 7.608 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-8M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 16.47 | 0.044 |
| Time | 26.81 | 0.0136 |
| Treatment | 32.59 | 0.0233 |
| Subjects (matching) | 10.22 | 0.2977 |

| *Source of Variation* | *P value summary* | *Significant?* |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 42.91 | 21.46 | 4.733 |
| Time | 2 | 69.87 | 34.93 | 7.705 |
| Treatment | 1 | 84.93 | 84.93 | 12.75 |
| Subjects (matching) | 4 | 26.64 | 6.659 | 1.469 |
| Residual | 8 | 36.27 | 4.534 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 15.7 | -1.267 | -7.160 to 4.627 |
| 1 | 17.27 | 8.7 | -8.567 | -14.46 to -2.673 |
| 2 | 19.27 | 16.07 | -3.2 | -9.094 to 2.694 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.267 | 0.6776 | P > 0.05 | ns |
| 1 | -8.567 | 4.582 | P<0.01 | ** |
| 2 | -3.2 | 1.712 | P > 0.05 | ns |

| | | |
|---|---|---|
| Table Analyzed | 10-8M Dectin-1 | |
| Two-way RM ANOVA | Matching by cols | |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 1.64 | 0.639 |
| Time | 75.46 | 0.0006 |
| Treatment | 5.61 | 0.0622 |
| Subjects (matching) | 3.4047 | 0.7435 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 3.914 | 1.957 | 0.4739 |
| Time | 2 | 179.6 | 89.78 | 21.74 |
| Treatment | 1 | 13.35 | 13.35 | 6.589 |
| Subjects (matching) | 4 | 8.102 | 2.026 | 0.4905 |
| Residual | 8 | 33.04 | 4.13 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 9.733 | -1.367 | -6.133 to 3.400 |
| 1 | 12.4 | 11.6 | -0.8 | -5.566 to 3.966 |
| 2 | 19.27 | 16.27 | -3 | -7.766 to 1.766 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.367 | 0.904 | P > 0.05 | ns |
| 1 | -0.8 | 0.5292 | P > 0.05 | ns |
| 2 | -3 | 1.984 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 9.99 | 0.1607 |
| Time | 11.79 | 0.1245 |
| Treatment | 22.08 | 0.2063 |
| Subjects (matching) | 38.8898 | 0.0336 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | * | Yes |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 8.608 | 4.304 | 2.317 |
| Time | 2 | 10.15 | 5.077 | 2.734 |
| Treatment | 1 | 19.01 | 19.01 | 2.271 |
| Subjects (matching) | 4 | 33.5 | 8.374 | 4.509 |
| Residual | 8 | 14.86 | 1.857 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

*Saline vs. Neo B*

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 14.43 | -0.9 | -6.067 to 4.267 |
| 1 | 17.27 | 16 | -1.267 | -6.434 to 3.901 |
| 2 | 17.27 | 13.27 | -4 | -9.167 to 1.167 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9 | 0.5491 | P > 0.05 | ns |
| 1 | -1.267 | 0.7728 | P > 0.05 | ns |
| 2 | -4 | 2.441 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 23.6 | 0.0651 |
| Time | 1.09 | 0.8372 |
| Treatment | 47.46 | 0.0021 |
| Subjects (matching) | 3.7633 | 0.862 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 20.29 | 10.14 | 3.918 |
| Time | 2 | 0.9411 | 0.4706 | 0.1818 |
| Treatment | 1 | 40.8 | 40.8 | 50.44 |
| Subjects (matching) | 4 | 3.236 | 0.8089 | 0.3124 |
| Residual | 8 | 20.71 | 2.589 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 15.2 | -1.767 | -5.403 to 1.870 |
| 1 | 17.27 | 16 | -1.267 | -4.903 to 2.370 |
| 2 | 19.27 | 13.27 | -6 | -9.636 to -2.364 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.767 | 1.532 | P > 0.05 | ns |
| 1 | -1.267 | 1.098 | P > 0.05 | ns |
| 2 | -6 | 5.202 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 0.6 | 0.4982 |
| Time | 0.52 | 0.5453 |
| Treatment | 93.43 | 0.0002 |
| Subjects (matching) | 2.295 | 0.3017 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 3.01 | 1.505 | 0.7611 |
| Time | 2 | 2.59 | 1.295 | 0.6549 |
| Treatment | 1 | 468.2 | 468.2 | 162.8 |
| Subjects (matching) | 4 | 11.5 | 2.875 | 1.454 |
| Residual | 8 | 15.82 | 1.978 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 7.9 | -9.067 | -12.95 to -5.183 |
| 1 | 17.17 | 6.2 | -10.97 | -14.85 to -7.083 |
| 2 | 16.87 | 6.3 | -10.57 | -14.45 to -6.683 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -9.067 | 7.359 | P<0.001 | *** |
| 1 | -10.97 | 8.902 | P<0.001 | *** |
| 2 | -10.57 | 8.577 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.19 | 0.4765 |
| Time | 2.38 | 0.4506 |
| Treatment | 80.25 | 0.001 |
| Subjects (matching) | 4.4051 | 0.5485 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 11.68 | 5.841 | 0.8143 |
| Time | 2 | 12.65 | 6.327 | 0.8822 |
| Treatment | 1 | 427.3 | 427.3 | 72.87 |
| Subjects (matching) | 4 | 23.46 | 5.864 | 0.8176 |
| Residual | 8 | 57.38 | 7.172 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 8.533 | -7.467 | -14.15 to -0.7857 |
| 1 | 17.27 | 6.433 | -10.83 | -17.51 to -4.152 |
| 2 | 19.27 | 8.333 | -10.93 | -17.61 to -4.252 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.467 | 3.523 | P < 0.05 | * |
| 1 | -10.83 | 5.112 | P<0.001 | *** |
| 2 | -10.93 | 5.159 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 13.88 | 0.0104 |
| Time | 6.85 | 0.0563 |
| Treatment | 69.93 | 0.0006 |
| Subjects (matching) | 2.8262 | 0.5227 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 65.54 | 32.77 | 8.527 |
| Time | 2 | 32.36 | 16.18 | 4.21 |
| Treatment | 1 | 330.2 | 330.2 | 98.97 |
| Subjects (matching) | 4 | 13.35 | 3.337 | 0.8682 |
| Residual | 8 | 30.75 | 3.843 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 13.7 | -3.267 | -8.201 to 1.668 |
| 1 | 17.27 | 6.933 | -10.33 | -15.27 to -5.399 |
| 2 | 19.27 | 7.167 | -12.1 | -17.03 to -7.166 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.267 | 2.087 | P > 0.05 | ns |
| 1 | -10.33 | 6.602 | P<0.001 | *** |
| 2 | -12.1 | 7.731 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 12.9 | 0.0392 |
| Time | 8.77 | 0.0857 |
| Treatment | 65.22 | 0.0006 |
| Subjects (matching) | 2.7725 | 0.7138 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 25.85 | 12.92 | 4.989 |
| Time | 2 | 17.57 | 8.787 | 3.392 |
| Treatment | 1 | 130.7 | 130.7 | 94.09 |
| Subjects (matching) | 4 | 5.556 | 1.389 | 0.5361 |
| Residual | 8 | 20.72 | 2.591 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 14.97 | -2 | -5.809 to 1.809 |
| 1 | 17.27 | 10.23 | -7.033 | -10.84 to -3.224 |
| 2 | 19.27 | 12.13 | -7.133 | -10.94 to -3.324 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2 | 1.655 | P > 0.05 | ns |
| 1 | -7.033 | 5.821 | P<0.001 | *** |
| 2 | -7.133 | 5.904 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 40.88 | 0.0015 |
| Time | 10.39 | 0.0583 |
| Treatment | 33.42 | 0.0073 |
| Subjects (matching) | 5.2741 | 0.4391 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 140.1 | 70.04 | 16.29 |
| Time | 2 | 35.58 | 17.79 | 4.139 |
| Treatment | 1 | 114.5 | 114.5 | 25.35 |
| Subjects (matching) | 4 | 18.07 | 4.518 | 1.051 |
| Residual | 8 | 34.39 | 4.299 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

*Saline vs. Neo B*

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 12.87 | 1.767 | -3.616 to 7.149 |
| 1 | 12.4 | 7.4 | -5 | -10.38 to 0.3822 |
| 2 | 19.27 | 7.367 | -11.9 | -17.28 to -6.518 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.767 | 1.035 | P > 0.05 | ns |
| 1 | -5 | 2.929 | P < 0.05 | * |
| 2 | -11.9 | 6.971 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.77 | 0.1306 |
| Time | 25.92 | 0.0022 |
| Treatment | 34.2 | 0.0914 |
| Subjects (matching) | 27.941 | 0.0073 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ** | Yes |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.738 | 3.369 | 2.654 |
| Time | 2 | 36.64 | 18.32 | 14.43 |
| Treatment | 1 | 48.35 | 48.35 | 4.895 |
| Subjects (matching) | 4 | 39.5 | 9.876 | 7.78 |
| Residual | 8 | 10.16 | 1.269 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

*Saline vs. Neo B*

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 10.77 | -4.567 | -9.803 to 0.6699 |
| 1 | 17.27 | 15.63 | -1.633 | -6.870 to 3.603 |
| 2 | 17.27 | 13.63 | -3.633 | -8.870 to 1.603 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.567 | 2.749 | P > 0.05 | ns |
| 1 | -1.633 | 0.9833 | P > 0.05 | ns |
| 2 | -3.633 | 2.187 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-10M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 18.03 | 0.0026 |
| Time | 28.92 | 0.0006 |
| Treatment | 45.98 | 0.0005 |
| Subjects (matching) | 1.7947 | 0.624 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 56.22 | 28.11 | 13.7 |
| Time | 2 | 90.17 | 45.09 | 21.97 |
| Treatment | 1 | 143.4 | 143.4 | 102.5 |
| Subjects (matching) | 4 | 5.596 | 1.399 | 0.6816 |
| Residual | 8 | 16.42 | 2.052 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 6.733 | -10.23 | -13.72 to -6.747 |
| 1 | 17.27 | 15.63 | -1.633 | -5.120 to 1.853 |
| 2 | 19.27 | 14.2 | -5.067 | -8.553 to -1.580 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -10.23 | 9.254 | P<0.001 | *** |
| 1 | -1.633 | 1.477 | P > 0.05 | ns |
| 2 | -5.067 | 4.582 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-10M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 20.4 | P<0.0001 |
| Time | 21.9 | P<0.0001 |
| Treatment | 54.61 | 0.0003 |
| Subjects (matching) | 1.6791 | 0.1383 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 150.6 | 75.31 | 57.75 |
| Time | 2 | 161.8 | 80.88 | 62.02 |
| Treatment | 1 | 403.3 | 403.3 | 130.1 |
| Subjects (matching) | 4 | 12.4 | 3.1 | 2.377 |
| Residual | 8 | 10.43 | 1.304 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 1.8 | -15.17 | -18.72 to -11.62 |
| 1 | 17.17 | 15.63 | -1.533 | -5.084 to 2.017 |
| 2 | 16.87 | 5.167 | -11.7 | -15.25 to -8.149 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -15.17 | 13.47 | P<0.001 | *** |
| 1 | -1.533 | 1.361 | P > 0.05 | ns |
| 2 | -11.7 | 10.39 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 14.97 | 0.0022 |
| Time | 25.09 | 0.0004 |
| Treatment | 51.98 | 0.0018 |
| Subjects (matching) | 3.7978 | 0.2178 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 94.1 | 47.05 | 14.37 |
| Time | 2 | 157.7 | 78.86 | 24.08 |
| Treatment | 1 | 326.8 | 326.8 | 54.75 |
| Subjects (matching) | 4 | 23.88 | 5.969 | 1.823 |
| Residual | 8 | 26.2 | 3.274 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 2.267 | -13.73 | -18.99 to -8.475 |
| 1 | 17.27 | 14.67 | -2.6 | -7.858 to 2.658 |
| 2 | 19.27 | 10.03 | -9.233 | -14.49 to -3.975 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -13.73 | 8.234 | P<0.001 | *** |
| 1 | -2.6 | 1.559 | P > 0.05 | ns |
| 2 | -9.233 | 5.536 | P<0.001 | *** |

| | | | | | |
|---|---|---|---|---|---|
| Table Analyzed | 10-10M Cdknlb | | | | |
| Two-way RM ANOVA | Matching by cols | | | | |
| Source of Variation | % of total variation | P value | | | |
| Interaction | 6.12 | 0.0153 | | | |
| Time | 8.72 | 0.0058 | | | |
| Treatment | 78.17 | 0.0008 | | | |
| Subjects (matching) | 3.6643 | 0.1588 | | | |
| Source of Variation | P value summary | Significant? | | | |
| Interaction | * | Yes | | | |
| Time | ** | Yes | | | |
| Treatment | *** | Yes | | | |
| Subjects (matching) | ns | No | | | |
| Source of Variation | Df | Sum-of-squares | Mean square | F | |
| Interaction | 2 | 34.4 | 17.2 | 7.365 | |
| Time | 2 | 48.95 | 24.48 | 10.48 | |
| Treatment | 1 | 439.1 | 439.1 | 85.33 | |
| Subjects (matching) | 4 | 20.58 | 5.146 | 2.203 | |
| Residual | 8 | 18.68 | 2.336 | | |
| Number of missing values | 0 | | | | |
| Bonferroni posttests | | | | | |
| *Saline vs. Neo B* | | | | | |
| Treatment | Saline | Neo B | Difference | 95% CI of diff. | |
| 0.5 | 16.97 | 4.167 | -12.8 | -17.46 to -8.144 | |
| 1 | 17.27 | 11.1 | -6.167 | -10.82 to -1.510 | |
| 2 | 19.27 | 8.6 | -10.67 | -15.32 to -6.010 | |
| Treatment | Difference | t | P value | Summary | |
| 0.5 | -12.8 | 8.666 | P<0.001 | *** | |
| 1 | -6.167 | 4.175 | P<0.01 | ** | |
| 2 | -10.67 | 7.222 | P<0.001 | *** | |

| | |
|---|---|
| Table Analyzed | 10-10M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 0.34 | 0.8961 |
| Time | 10.51 | 0.0841 |
| Treatment | 72.83 | 0.0011 |
| Subjects (matching) | 4.0534 | 0.6362 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 0.4544 | 0.2272 | 0.1112 |
| Time | 2 | 14.01 | 7.004 | 3.428 |
| Treatment | 1 | 97.07 | 97.07 | 71.87 |
| Subjects (matching) | 4 | 5.402 | 1.351 | 0.661 |
| Residual | 8 | 16.34 | 2.043 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 12.4 | -4.567 | -8.032 to -1.101 |
| 1 | 17.27 | 12.97 | -4.3 | -7.765 to -0.8347 |
| 2 | 19.27 | 14.2 | -5.067 | -8.532 to -1.601 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.567 | 4.155 | P<0.01 | ** |
| 1 | -4.3 | 3.912 | P<0.01 | ** |
| 2 | -5.067 | 4.61 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-10M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 29.41 | 0.006 |
| Time | 19.87 | 0.0175 |
| Treatment | 35.82 | 0.0031 |
| Subjects (matching) | 3.5425 | 0.6588 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 72.98 | 36.49 | 10.35 |
| Time | 2 | 49.3 | 24.65 | 6.994 |
| Treatment | 1 | 88.89 | 88.89 | 40.44 |
| Subjects (matching) | 4 | 8.791 | 2.198 | 0.6236 |
| Residual | 8 | 28.2 | 3.524 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 9.267 | -1.833 | -6.353 to 2.686 |
| 1 | 12.4 | 11.03 | -1.367 | -5.886 to 3.153 |
| 2 | 19.27 | 9.133 | -10.13 | -14.65 to -5.614 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.833 | 1.279 | P > 0.05 | ns |
| 1 | -1.367 | 0.9534 | P > 0.05 | ns |
| 2 | -10.13 | 7.069 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 0.57 | 0.8497 |
| Time | 21.92 | 0.0223 |
| Treatment | 21.84 | 0.2221 |
| Subjects (matching) | 41.8595 | 0.0152 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ns | No |
| Subjects (matching) | * | Yes |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 0.4678 | 0.2339 | 0.1662 |
| Time | 2 | 17.87 | 8.934 | 6.349 |
| Treatment | 1 | 17.8 | 17.8 | 2.087 |
| Subjects (matching) | 4 | 34.12 | 8.531 | 6.062 |
| Residual | 8 | 11.26 | 1.407 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 13.13 | -2.2 | -7.206 to 2.806 |
| 1 | 17.27 | 15.03 | -2.233 | -7.239 to 2.772 |
| 2 | 17.27 | 15.73 | -1.533 | -6.539 to 3.472 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.2 | 1.386 | P > 0.05 | ns |
| 1 | -2.233 | 1.407 | P > 0.05 | ns |
| 2 | -1.533 | 0.9657 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 11.76 | 0.0237 |
| Time | 29.84 | 0.0017 |
| Treatment | 48.86 | 0.0006 |
| Subjects (matching) | 1.948 | 0.7289 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 29.91 | 14.96 | 6.192 |
| Time | 2 | 75.9 | 37.95 | 15.71 |
| Treatment | 1 | 124.3 | 124.3 | 100.3 |
| Subjects (matching) | 4 | 4.956 | 1.239 | 0.5129 |
| Residual | 8 | 19.32 | 2.416 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 8.067 | -8.9 | -12.56 to -5.238 |
| 1 | 17.27 | 13.93 | -3.333 | -6.995 to 0.3282 |
| 2 | 19.27 | 15.73 | -3.533 | -7.195 to 0.1282 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -8.9 | 7.663 | P<0.001 | *** |
| 1 | -3.333 | 2.87 | P < 0.05 | * |
| 2 | -3.533 | 3.042 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-11M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 7.45 | 0.0025 |
| Time | 7.1 | 0.0029 |
| Treatment | 80.49 | 0.0004 |
| Subjects (matching) | 2.8208 | 0.113 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 46.83 | 23.42 | 13.96 |
| Time | 2 | 44.59 | 22.3 | 13.29 |
| Treatment | 1 | 505.6 | 505.6 | 114.1 |
| Subjects (matching) | 4 | 17.72 | 4.43 | 2.641 |
| Residual | 8 | 13.42 | 1.678 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 2.467 | -14.5 | -18.65 to -10.35 |
| 1 | 17.17 | 6.467 | -10.7 | -14.85 to -6.553 |
| 2 | 16.87 | 10.27 | -6.6 | -10.75 to -2.453 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -14.5 | 11.02 | P<0.001 | *** |
| 1 | -10.7 | 8.135 | P<0.001 | *** |
| 2 | -6.6 | 5.018 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 6.97 | 0.0076 |
| Time | 23.08 | 0.0002 |
| Treatment | 65.04 | 0.0003 |
| Subjects (matching) | 1.9997 | 0.3257 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 47.89 | 23.95 | 9.548 |
| Time | 2 | 158.6 | 79.31 | 31.62 |
| Treatment | 1 | 447 | 447 | 130.1 |
| Subjects (matching) | 4 | 13.74 | 3.436 | 1.37 |
| Residual | 8 | 20.06 | 2.508 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 2.8 | -13.2 | -17.52 to -8.879 |
| 1 | 17.27 | 6.067 | -11.2 | -15.52 to -6.879 |
| 2 | 19.27 | 13.77 | -5.5 | -9.821 to -1.179 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -13.2 | 9.632 | P<0.001 | *** |
| 1 | -11.2 | 8.172 | P<0.001 | *** |
| 2 | -5.5 | 4.013 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-11M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.76 | 0.0272 |
| Time | 16.42 | 0.0014 |
| Treatment | 72.98 | P<0.0001 |
| Subjects (matching) | 0.8869 | 0.7704 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 34.29 | 17.14 | 5.848 |
| Time | 2 | 97.69 | 48.85 | 16.66 |
| Treatment | 1 | 434.1 | 434.1 | 329.2 |
| Subjects (matching) | 4 | 5.276 | 1.319 | 0.4499 |
| Residual | 8 | 23.45 | 2.931 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 3.6 | -13.37 | -17.35 to -9.384 |
| 1 | 17.27 | 7.8 | -9.467 | -13.45 to -5.484 |
| 2 | 19.27 | 12.63 | -6.633 | -10.62 to -2.651 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -13.37 | 10.58 | P<0.001 | *** |
| 1 | -9.467 | 7.494 | P<0.001 | *** |
| 2 | -6.633 | 5.251 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-11M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 3.1 | 0.4088 |
| Time | 22.23 | 0.0163 |
| Treatment | 58.92 | 0.0011 |
| Subjects (matching) | 3.3747 | 0.7076 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 5.23 | 2.615 | 1.003 |
| Time | 2 | 37.51 | 18.75 | 7.19 |
| Treatment | 1 | 99.41 | 99.41 | 69.84 |
| Subjects (matching) | 4 | 5.693 | 1.423 | 0.5457 |
| Residual | 8 | 20.87 | 2.608 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 12.53 | -4.433 | -7.810 to -1.057 |
| 1 | 17.27 | 11.13 | -6.133 | -9.510 to -2.757 |
| 2 | 19.27 | 15.73 | -3.533 | -6.910 to -0.1571 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.433 | 3.65 | P<0.01 | ** |
| 1 | -6.133 | 5.049 | P<0.001 | *** |
| 2 | -3.533 | 2.909 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-11M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 8.58 | 0.0904 |
| Time | 42.97 | 0.0014 |
| Treatment | 33.34 | 0.006 |
| Subjects (matching) | 4.6908 | 0.5067 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 24.98 | 12.49 | 3.295 |
| Time | 2 | 125.1 | 62.56 | 16.5 |
| Treatment | 1 | 97.07 | 97.07 | 28.43 |
| Subjects (matching) | 4 | 13.66 | 3.414 | 0.9006 |
| Residual | 8 | 30.33 | 3.791 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 9.567 | -1.533 | -6.462 to 3.395 |
| 1 | 12.4 | 7.233 | -5.167 | -10.10 to -0.2383 |
| 2 | 19.27 | 12.03 | -7.233 | -12.16 to -2.305 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.533 | 0.9809 | P > 0.05 | ns |
| 1 | -5.167 | 3.305 | P < 0.05 | * |
| 2 | -7.233 | 4.627 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-12M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 0.35 | 0.9353 |
| Time | 19.35 | 0.0704 |
| Treatment | 1.12 | 0.7961 |
| Subjects (matching) | 58.6328 | 0.018 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | * | Yes |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 0.2233 | 0.1117 | 0.06746 |
| Time | 2 | 12.47 | 6.234 | 3.766 |
| Treatment | 1 | 0.72 | 0.72 | 0.07624 |
| Subjects (matching) | 4 | 37.78 | 9.444 | 5.706 |
| Residual | 8 | 13.24 | 1.655 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

*Saline vs. Neo B*

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.33 | 15.17 | -0.1667 | -5.474 to 5.141 |
| 1 | 17.27 | 16.57 | -0.7 | -6.008 to 4.608 |
| 2 | 17.27 | 16.93 | -0.3333 | -5.641 to 4.974 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1667 | 0.09899 | P > 0.05 | ns |
| 1 | -0.7 | 0.4158 | P > 0.05 | ns |
| 2 | -0.3333 | 0.198 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.76 | 0.4988 |
| Time | 30.37 | 0.011 |
| Treatment | 44.81 | 0.0081 |
| Subjects (matching) | 7.4947 | 0.448 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 3.488 | 1.744 | 0.7597 |
| Time | 2 | 38.32 | 19.16 | 8.347 |
| Treatment | 1 | 56.53 | 56.53 | 23.92 |
| Subjects (matching) | 4 | 9.456 | 2.364 | 1.03 |
| Residual | 8 | 18.36 | 2.296 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 12.57 | -4.4 | -8.319 to -0.4806 |
| 1 | 17.27 | 13.37 | -3.9 | -7.819 to 0.01942 |
| 2 | 19.27 | 16.93 | -2.333 | -6.253 to 1.586 |

| *Treatment* | *Difference* | *t* | *P value* | *Summary* |
|---|---|---|---|---|
| 0.5 | -4.4 | 3.539 | P < 0.05 | * |
| 1 | -3.9 | 3.137 | P < 0.05 | * |
| 2 | -2.333 | 1.877 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 9.43 | 0.005 |
| Time | 8.31 | 0.0072 |
| Treatment | 74.78 | 0.001 |
| Subjects (matching) | 4.057 | 0.1389 |

| *Source of Variation* | *P value summary* | *Significant?* |
|---|---|---|
| Interaction | ** | Yes |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 49.29 | 24.64 | 11.02 |
| Time | 2 | 43.48 | 21.74 | 9.721 |
| Treatment | 1 | 391.1 | 391.1 | 73.73 |
| Subjects (matching) | 4 | 21.22 | 5.304 | 2.372 |
| Residual | 8 | 17.89 | 2.236 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 5.733 | -11.23 | -15.88 to -6.586 |
| 1 | 17.17 | 5.1 | -12.07 | -16.71 to -7.420 |
| 2 | 16.87 | 12.2 | -4.667 | -9.314 to -0.01971 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -11.23 | 7.621 | P<0.001 | *** |
| 1 | -12.07 | 8.186 | P<0.001 | *** |
| 2 | -4.667 | 3.166 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-12M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.61 | 0.1228 |
| Time | 17.37 | 0.006 |
| Treatment | 68.12 | 0.0008 |
| Subjects (matching) | 3.2192 | 0.4773 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 20.35 | 10.18 | 2.757 |
| Time | 2 | 76.75 | 38.38 | 10.4 |
| Treatment | 1 | 300.9 | 300.9 | 84.64 |
| Subjects (matching) | 4 | 14.22 | 3.556 | 0.9634 |
| Residual | 8 | 29.52 | 3.691 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16 | 8.333 | -7.667 | -12.58 to -2.752 |
| 1 | 17.27 | 6.267 | -11 | -15.91 to -6.085 |
| 2 | 19.27 | 13.4 | -5.867 | -10.78 to -0.9518 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.667 | 4.918 | P<0.01 | ** |
| 1 | -11 | 7.056 | P<0.001 | *** |
| 2 | -5.867 | 3.763 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-12M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.2 | 0.3593 |
| Time | 9.09 | 0.0421 |
| Treatment | 78.1 | 0.0005 |
| Subjects (matching) | 3.0844 | 0.5476 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 8.074 | 4.037 | 1.167 |
| Time | 2 | 33.42 | 16.71 | 4.829 |
| Treatment | 1 | 287.2 | 287.2 | 101.3 |
| Subjects (matching) | 4 | 11.34 | 2.836 | 0.8194 |
| Residual | 8 | 27.68 | 3.461 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 10.13 | -6.833 | -11.48 to -2.191 |
| 1 | 17.27 | 7.4 | -9.867 | -14.51 to -5.224 |
| 2 | 19.27 | 12 | -7.267 | -11.91 to -2.624 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6.833 | 4.641 | P<0.01 | ** |
| 1 | -9.867 | 6.701 | P<0.001 | *** |
| 2 | -7.267 | 4.935 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-12M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 10.81 | 0.0989 |
| Time | 30.86 | 0.0091 |
| Treatment | 38.58 | 0.007 |
| Subjects (matching) | 5.9424 | 0.5263 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 15.74 | 7.872 | 3.133 |
| Time | 2 | 44.94 | 22.47 | 8.944 |
| Treatment | 1 | 56.18 | 56.18 | 25.97 |
| Subjects (matching) | 4 | 8.653 | 2.163 | 0.861 |
| Residual | 8 | 20.1 | 2.513 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 16.97 | 14.97 | -2 | -5.985 to 1.985 |
| 1 | 17.27 | 11.1 | -6.167 | -10.15 to -2.182 |
| 2 | 19.27 | 16.83 | -2.433 | -6.418 to 1.551 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2 | 1.582 | P > 0.05 | ns |
| 1 | -6.167 | 4.879 | P<0.01 | ** |
| 2 | -2.433 | 1.925 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.04 | 0.224 |
| Time | 55.03 | 0.0008 |
| Treatment | 27.74 | 0.0005 |
| Subjects (matching) | 1.0724 | 0.9353 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 13.67 | 6.837 | 1.814 |
| Time | 2 | 149.3 | 74.63 | 19.8 |
| Treatment | 1 | 75.24 | 75.24 | 103.5 |
| Subjects (matching) | 4 | 2.909 | 0.7272 | 0.193 |
| Residual | 8 | 30.15 | 3.769 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. Neo B

| Treatment | Saline | Neo B | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.1 | 9.333 | -1.767 | -6.039 to 2.506 |
| 1 | 12.4 | 7.867 | -4.533 | -8.806 to -0.2607 |
| 2 | 19.27 | 13.3 | -5.967 | -10.24 to -1.694 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.767 | 1.304 | P > 0.05 | ns |
| 1 | -4.533 | 3.345 | P < 0.05 | * |
| 2 | -5.967 | 4.403 | P<0.01 | ** |

# APPENDIX III – ANOVA TABLES ß (1,3) GLUCAN

| | |
|---|---|
| Table Analyzed | 10-8M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 39.73 | 0.0052 |
| Time | 25.01 | 0.0185 |
| Treatment | 17.15 | 0.0113 |
| Subjects (matching) | 3.4779 | 0.7532 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| *Source of Variation* | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 47.93 | 23.97 | 10.87 |
| Time | 2 | 30.17 | 15.09 | 6.843 |
| Treatment | 1 | 20.69 | 20.69 | 19.73 |
| Subjects (matching) | 4 | 4.196 | 1.049 | 0.4757 |
| Residual | 8 | 17.64 | 2.205 | |

| | |
|---|---|
| Number of missing values | 0 |

*Bonferroni posttests*

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.83 | 13.8 | 2.967 | -0.5055 to 6.439 |
| 1 | 11.97 | 17.63 | 5.667 | 2.194 to 9.139 |
| 2 | 16.37 | 14.17 | -2.2 | -5.672 to 1.272 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.967 | 2.694 | P > 0.05 | ns |
| 1 | 5.667 | 5.145 | P<0.001 | *** |
| 2 | -2.2 | 1.998 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Hspb1 |
| Two-way RM ANOVA | *Matching by cols* |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 27.07 | 0.0683 |
| Time | 7.17 | 0.4056 |
| Treatment | 16.53 | 0.1501 |
| Subjects (matching) | 20.9192 | 0.2953 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 13.1 | 6.552 | 3.825 |
| Time | 2 | 3.468 | 1.734 | 1.012 |
| Treatment | 1 | 8 | 8 | 3.161 |
| Subjects (matching) | 4 | 10.12 | 2.531 | 1.478 |
| Residual | 8 | 13.7 | 1.713 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.13 | 18.8 | 3.667 | 0.03944 to 7.294 |
| 1 | 17.03 | 17.73 | 0.7 | -2.927 to 4.327 |
| 2 | 16.5 | 16.13 | -0.3667 | -3.994 to 3.261 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.667 | 3.187 | P < 0.05 | * |
| 1 | 0.7 | 0.6084 | P > 0.05 | ns |
| 2 | -0.3667 | 0.3187 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 31.22 | 0.0029 |
| Time | 28.71 | 0.0038 |
| Treatment | 21.49 | 0.0373 |
| Subjects (matching) | 9.1299 | 0.1983 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 78.54 | 39.27 | 13.22 |
| Time | 2 | 72.25 | 36.12 | 12.16 |
| Treatment | 1 | 54.08 | 54.08 | 9.417 |
| Subjects (matching) | 4 | 22.97 | 5.743 | 1.933 |
| Residual | 8 | 23.76 | 2.97 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.033 | 9.467 | 3.433 | -1.647 to 8.513 |
| 1 | 7.133 | 15.73 | 8.6 | 3.520 to 13.68 |
| 2 | 7.6 | 5.967 | -1.633 | -6.713 to 3.447 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.433 | 2.131 | P > 0.05 | ns |
| 1 | 8.6 | 5.337 | P<0.001 | *** |
| 2 | -1.633 | 1.014 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 72.47 | 0.0009 |
| Time | 4.61 | 0.346 |
| Treatment | 2.39 | 0.2517 |
| Subjects (matching) | 5.3404 | 0.6113 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 80.12 | 40.06 | 19.09 |
| Time | 2 | 5.101 | 2.551 | 1.215 |
| Treatment | 1 | 2.645 | 2.645 | 1.792 |
| Subjects (matching) | 4 | 5.904 | 1.476 | 0.7034 |
| Residual | 8 | 16.79 | 2.099 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 11.3 | 3.833 | 0.2934 to 7.373 |
| 1 | 7.8 | 11.47 | 3.667 | 0.1268 to 7.207 |
| 2 | 11 | 5.8 | -5.2 | -8.740 to -1.660 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.833 | 3.414 | P < 0.05 | * |
| 1 | 3.667 | 3.266 | P < 0.05 | * |
| 2 | -5.2 | 4.631 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-8M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 40.94 | 0.0009 |
| Time | 11.28 | 0.0336 |
| Treatment | 31.65 | 0.0154 |
| Subjects (matching) | 7.6897 | 0.2179 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 72.21 | 36.1 | 19.4 |
| Time | 2 | 19.89 | 9.944 | 5.345 |
| Treatment | 1 | 55.83 | 55.83 | 16.47 |
| Subjects (matching) | 4 | 13.56 | 3.391 | 1.822 |
| Residual | 8 | 14.88 | 1.861 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.133 | 13.2 | 4.067 | 0.1033 to 8.030 |
| 1 | 9.6 | 17.73 | 8.133 | 4.170 to 12.10 |
| 2 | 13.77 | 12.13 | -1.633 | -5.597 to 2.330 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.067 | 3.235 | P < 0.05 | * |
| 1 | 8.133 | 6.47 | P<0.001 | *** |
| 2 | -1.633 | 1.299 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 0.42 | 0.9408 |
| Time | 12.51 | 0.222 |
| Treatment | 21.46 | 0.2083 |
| Subjects (matching) | 38.209 | 0.1012 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 0.1678 | 0.08389 | 0.06154 |
| Time | 2 | 4.981 | 2.491 | 1.827 |
| Treatment | 1 | 8.542 | 8.542 | 2.247 |
| Subjects (matching) | 4 | 15.21 | 3.802 | 2.789 |
| Residual | 8 | 10.9 | 1.363 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 17.37 | 19 | 1.633 | -2.164 to 5.431 |
| 1 | 16.57 | 17.73 | 1.167 | -2.631 to 4.964 |
| 2 | 16.33 | 17.67 | 1.333 | -2.464 to 5.131 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.633 | 1.356 | P > 0.05 | ns |
| 1 | 1.167 | 0.9686 | P > 0.05 | ns |
| 2 | 1.333 | 1.107 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-8M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 41.01 | P<0.0001 |
| Time | 34.54 | P<0.0001 |
| Treatment | 18.27 | 0.0091 |
| Subjects (matching) | 3.2619 | 0.1552 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 79.82 | 39.91 | 56.1 |
| Time | 2 | 67.22 | 33.61 | 47.24 |
| Treatment | 1 | 35.56 | 35.56 | 22.4 |
| Subjects (matching) | 4 | 6.349 | 1.587 | 2.231 |
| Residual | 8 | 5.691 | 0.7114 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.13 | 10.9 | -0.2333 | -2.812 to 2.345 |
| 1 | 15.8 | 15.7 | -0.1 | -2.678 to 2.478 |
| 2 | 8.967 | 17.73 | 8.767 | 6.188 to 11.35 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.2333 | 0.2853 | P > 0.05 | ns |
| 1 | -0.1 | 0.1223 | P > 0.05 | ns |
| 2 | 8.767 | 10.72 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 20.97 | 0.0208 |
| Time | 49.41 | 0.0018 |
| Treatment | 15.78 | 0.0014 |
| Subjects (matching) | 1.0055 | 0.9545 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 16.17 | 8.087 | 6.532 |
| Time | 2 | 38.11 | 19.05 | 15.39 |
| Treatment | 1 | 12.17 | 12.17 | 62.76 |
| Subjects (matching) | 4 | 0.7756 | 0.1939 | 0.1566 |
| Residual | 8 | 9.904 | 1.238 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.83 | 13.93 | 3.1 | 0.6716 to 5.528 |
| 1 | 11.97 | 14.83 | 2.867 | 0.4382 to 5.295 |
| 2 | 16.37 | 15.33 | -1.033 | -3.462 to 1.395 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.1 | 4.025 | P<0.01 | ** |
| 1 | 2.867 | 3.722 | P<0.01 | ** |
| 2 | -1.033 | 1.342 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 3.69 | 0.7171 |
| Time | 37.29 | 0.0805 |
| Treatment | 13.05 | 0.0178 |
| Subjects (matching) | 3.4635 | 0.9513 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 0.8133 | 0.4067 | 0.3468 |
| Time | 2 | 8.231 | 4.116 | 3.509 |
| Treatment | 1 | 2.88 | 2.88 | 15.07 |
| Subjects (matching) | 4 | 0.7644 | 0.1911 | 0.163 |
| Residual | 8 | 9.382 | 1.173 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

*Saline vs. glucan*

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.13 | 14.6 | -0.5333 | -2.900 to 1.834 |
| 1 | 17.03 | 15.63 | -1.4 | -3.767 to 0.9670 |
| 2 | 16.5 | 16.03 | -0.4667 | -2.834 to 1.900 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5333 | 0.7104 | P > 0.05 | ns |
| 1 | -1.4 | 1.865 | P > 0.05 | ns |
| 2 | -0.4667 | 0.6216 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 50.26 | 0.0103 |
| Time | 10.76 | 0.2215 |
| Treatment | 4.84 | 0.2488 |
| Subjects (matching) | 10.6387 | 0.5045 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 4.21 | 2.105 | 8.553 |
| Time | 2 | 0.9011 | 0.4506 | 1.831 |
| Treatment | 1 | 0.405 | 0.405 | 1.818 |
| Subjects (matching) | 4 | 0.8911 | 0.2228 | 0.9052 |
| Residual | 8 | 1.969 | 0.2461 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.033 | 7.1 | 1.067 | -0.1900 to 2.323 |
| 1 | 7.133 | 6.2 | -0.9333 | -2.190 to 0.3234 |
| 2 | 7.6 | 6.567 | -1.033 | -2.290 to 0.2234 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.067 | 2.676 | P > 0.05 | ns |
| 1 | -0.9333 | 2.341 | P > 0.05 | ns |
| 2 | -1.033 | 2.592 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-9M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 18.21 | 0.0753 |
| Time | 31.85 | 0.0222 |
| Treatment | 22.21 | 0.0274 |
| Subjects (matching) | 7.701 | 0.5746 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 8.551 | 4.276 | 3.637 |
| Time | 2 | 14.95 | 7.476 | 6.359 |
| Treatment | 1 | 10.43 | 10.43 | 11.54 |
| Subjects (matching) | 4 | 3.616 | 0.9039 | 0.7689 |
| Residual | 8 | 9.404 | 1.176 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 7.233 | -0.2333 | -2.915 to 2.448 |
| 1 | 7.8 | 6.9 | -0.9 | -3.581 to 1.781 |
| 2 | 11 | 7.567 | -3.433 | -6.115 to -0.7520 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.2333 | 0.2744 | P > 0.05 | ns |
| 1 | -0.9 | 1.058 | P > 0.05 | ns |
| 2 | -3.433 | 4.037 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-9M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 41.04 | 0.0005 |
| Time | 29.09 | 0.0016 |
| Treatment | 20.82 | 0.0024 |
| Subjects (matching) | 1.7985 | 0.7396 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | ** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 23.02 | 11.51 | 22.66 |
| Time | 2 | 16.32 | 8.161 | 16.06 |
| Treatment | 1 | 11.68 | 11.68 | 46.31 |
| Subjects (matching) | 4 | 1.009 | 0.2522 | 0.4964 |
| Residual | 8 | 4.064 | 0.5081 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.133 | 9.333 | 0.2 | -1.474 to 1.874 |
| 1 | 9.6 | 9.367 | -0.2333 | -1.907 to 1.440 |
| 2 | 13.77 | 8.967 | -4.8 | -6.474 to -3.126 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2 | 0.3767 | P > 0.05 | ns |
| 1 | -0.2333 | 0.4395 | P > 0.05 | ns |
| 2 | -4.8 | 9.041 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-9M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 11.34 | 0.2413 |
| Time | 25.56 | 0.0675 |
| Treatment | 27.12 | 0.0274 |
| Subjects (matching) | 9.4077 | 0.6086 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 2.914 | 1.457 | 1.707 |
| Time | 2 | 6.57 | 3.285 | 3.848 |
| Treatment | 1 | 6.969 | 6.969 | 11.53 |
| Subjects (matching) | 4 | 2.418 | 0.6044 | 0.7081 |
| Residual | 8 | 6.829 | 0.8536 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 17.37 | 15.9 | -1.467 | -3.726 to 0.7930 |
| 1 | 16.57 | 16.4 | -0.1667 | -2.426 to 2.093 |
| 2 | 16.33 | 14.23 | -2.1 | -4.360 to 0.1596 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.467 | 2.046 | P > 0.05 | ns |
| 1 | -0.1667 | 0.2325 | P > 0.05 | ns |
| 2 | -2.1 | 2.93 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-9M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 12.24 | 0.0025 |
| Time | 51.95 | P<0.0001 |
| Treatment | 31 | 0.0006 |
| Subjects (matching) | 1.2978 | 0.5913 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 17.94 | 8.969 | 13.93 |
| Time | 2 | 76.14 | 38.07 | 59.12 |
| Treatment | 1 | 45.44 | 45.44 | 95.56 |
| Subjects (matching) | 4 | 1.902 | 0.4756 | 0.7386 |
| Residual | 8 | 5.151 | 0.6439 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.13 | 9.867 | -1.267 | -3.240 to 0.7069 |
| 1 | 15.8 | 9.867 | -5.933 | -7.907 to -3.960 |
| 2 | 8.967 | 6.633 | -2.333 | -4.307 to -0.3598 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.267 | 2.023 | P > 0.05 | ns |
| 1 | -5.933 | 9.478 | P<0.001 | *** |
| 2 | -2.333 | 3.727 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-10M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.06 | 0.0756 |
| Time | 82.68 | P<0.0001 |
| Treatment | 0.04 | 0.8777 |
| Subjects (matching) | 6.6362 | 0.138 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 4.031 | 2.016 | 3.628 |
| Time | 2 | 65.9 | 32.95 | 59.31 |
| Treatment | 1 | 0.03556 | 0.03556 | 0.02689 |
| Subjects (matching) | 4 | 5.289 | 1.322 | 2.38 |
| Residual | 8 | 4.444 | 0.5556 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.83 | 11.63 | 0.8 | -1.518 to 3.118 |
| 1 | 11.97 | 12.3 | 0.3333 | -1.985 to 2.652 |
| 2 | 16.37 | 14.97 | -1.4 | -3.718 to 0.9183 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.8 | 1.088 | P > 0.05 | ns |
| 1 | 0.3333 | 0.4533 | P > 0.05 | ns |
| 2 | -1.4 | 1.904 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-10M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.6 | 0.6798 |
| Time | 26.98 | 0.1546 |
| Treatment | 20.49 | 0.0049 |
| Subjects (matching) | 2.5784 | 0.9741 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 1.101 | 0.5506 | 0.4052 |
| Time | 2 | 6.463 | 3.232 | 2.379 |
| Treatment | 1 | 4.909 | 4.909 | 31.78 |
| Subjects (matching) | 4 | 0.6178 | 0.1544 | 0.1137 |
| Residual | 8 | 10.87 | 1.359 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.13 | 14.77 | -0.3667 | -2.885 to 2.152 |
| 1 | 17.03 | 15.8 | -1.233 | -3.752 to 1.285 |
| 2 | 16.5 | 14.97 | -1.533 | -4.052 to 0.9852 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.3667 | 0.459 | P > 0.05 | ns |
| 1 | -1.233 | 1.544 | P > 0.05 | ns |
| 2 | -1.533 | 1.919 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-10M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 31.41 | 0.0869 |
| Time | 21.47 | 0.1624 |
| Treatment | 6.25 | 0.0564 |
| Subjects (matching) | 3.5366 | 0.9372 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 4.243 | 2.122 | 3.366 |
| Time | 2 | 2.901 | 1.451 | 2.301 |
| Treatment | 1 | 0.845 | 0.845 | 7.074 |
| Subjects (matching) | 4 | 0.4778 | 0.1194 | 0.1895 |
| Residual | 8 | 5.042 | 0.6303 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.033 | 6.4 | 0.3667 | -1.379 to 2.113 |
| 1 | 7.133 | 7.267 | 0.1333 | -1.613 to 1.879 |
| 2 | 7.6 | 5.8 | -1.8 | -3.546 to -0.05413 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.3667 | 0.6621 | P > 0.05 | ns |
| 1 | 0.1333 | 0.2408 | P > 0.05 | ns |
| 2 | -1.8 | 3.25 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-10M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 13.87 | 0.1334 |
| Time | 42.57 | 0.0122 |
| Treatment | 14.33 | 0.0558 |
| Subjects (matching) | 8.0451 | 0.5797 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.041 | 3.021 | 2.618 |
| Time | 2 | 18.54 | 9.272 | 8.037 |
| Treatment | 1 | 6.242 | 6.242 | 7.125 |
| Subjects (matching) | 4 | 3.504 | 0.8761 | 0.7595 |
| Residual | 8 | 9.229 | 1.154 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 7.3 | -0.1667 | -2.818 to 2.485 |
| 1 | 7.8 | 7.233 | -0.5667 | -3.218 to 2.085 |
| 2 | 11 | 8.2 | -2.8 | -5.452 to -0.1484 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1667 | 0.1982 | P > 0.05 | ns |
| 1 | -0.5667 | 0.6737 | P > 0.05 | ns |
| 2 | -2.8 | 3.329 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-10M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| *Source of Variation* | *% of total variation* | P value |
|---|---|---|
| Interaction | 36.32 | 0.0038 |
| Time | 36.2 | 0.0038 |
| Treatment | 12.38 | 0.0163 |
| Subjects (matching) | 3.1108 | 0.7247 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 19.72 | 9.861 | 12.13 |
| Time | 2 | 19.65 | 9.827 | 12.09 |
| Treatment | 1 | 6.722 | 6.722 | 15.92 |
| Subjects (matching) | 4 | 1.689 | 0.4222 | 0.5193 |
| Residual | 8 | 6.504 | 0.8131 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.133 | 9.833 | 0.7 | -1.427 to 2.827 |
| 1 | 9.6 | 9.367 | -0.2333 | -2.360 to 1.894 |
| 2 | 13.77 | 9.633 | -4.133 | -6.260 to -2.006 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7 | 1.038 | P > 0.05 | ns |
| 1 | -0.2333 | 0.3458 | P > 0.05 | ns |
| 2 | -4.133 | 6.126 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | 10-10M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 15.43 | 0.1184 |
| Time | 20.68 | 0.0699 |
| Treatment | 35.82 | 0.0085 |
| Subjects (matching) | 6.1781 | 0.6957 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.914 | 3.457 | 2.819 |
| Time | 2 | 9.268 | 4.634 | 3.778 |
| Treatment | 1 | 16.06 | 16.06 | 23.19 |
| Subjects (matching) | 4 | 2.769 | 0.6922 | 0.5644 |
| Residual | 8 | 9.811 | 1.226 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 17.37 | 14.9 | -2.467 | -5.102 to 0.1690 |
| 1 | 16.57 | 16.4 | -0.1667 | -2.802 to 2.469 |
| 2 | 16.33 | 13.3 | -3.033 | -5.669 to -0.3977 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.467 | 2.951 | P < 0.05 | * |
| 1 | -0.1667 | 0.1994 | P > 0.05 | ns |
| 2 | -3.033 | 3.628 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-10M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 11.28 | 0.0019 |
| Time | 45.8 | P<0.0001 |
| Treatment | 39.13 | 0.0002 |
| Subjects (matching) | 0.797 | 0.7159 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 17.87 | 8.934 | 15.09 |
| Time | 2 | 72.53 | 36.27 | 61.24 |
| Treatment | 1 | 61.98 | 61.98 | 196.4 |
| Subjects (matching) | 4 | 1.262 | 0.3156 | 0.5328 |
| Residual | 8 | 4.738 | 0.5922 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.13 | 9.167 | -1.967 | -3.787 to -0.1465 |
| 1 | 15.8 | 9.3 | -6.5 | -8.320 to -4.680 |
| 2 | 8.967 | 6.3 | -2.667 | -4.487 to -0.8465 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.967 | 3.406 | P < 0.05 | * |
| 1 | -6.5 | 11.26 | P<0.001 | *** |
| 2 | -2.667 | 4.619 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-11M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 7.22 | 0.3435 |
| Time | 54.34 | 0.0084 |
| Treatment | 2.49 | 0.4204 |
| Subjects (matching) | 12.3862 | 0.4389 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 8.108 | 4.054 | 1.225 |
| Time | 2 | 61.06 | 30.53 | 9.226 |
| Treatment | 1 | 2.801 | 2.801 | 0.8049 |
| Subjects (matching) | 4 | 13.92 | 3.479 | 1.051 |
| Residual | 8 | 26.48 | 3.309 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.83 | 11.97 | 1.133 | -3.589 to 5.856 |
| 1 | 11.97 | 14.2 | 2.233 | -2.489 to 6.956 |
| 2 | 16.37 | 15.37 | -1 | -5.723 to 3.723 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.133 | 0.7566 | P > 0.05 | ns |
| 1 | 2.233 | 1.491 | P > 0.05 | ns |
| 2 | -1 | 0.6675 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 10.75 | 0.4328 |
| Time | 3.01 | 0.777 |
| Treatment | 12.83 | 0.2419 |
| Subjects (matching) | 27.2565 | 0.3883 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.37 | 3.185 | 0.9317 |
| Time | 2 | 1.781 | 0.8906 | 0.2605 |
| Treatment | 1 | 7.605 | 7.605 | 1.883 |
| Subjects (matching) | 4 | 16.15 | 4.038 | 1.181 |
| Residual | 8 | 27.35 | 3.419 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.13 | 15.2 | 0.06667 | -4.834 to 4.968 |
| 1 | 17.03 | 14.2 | -2.833 | -7.734 to 2.068 |
| 2 | 16.5 | 15.37 | -1.133 | -6.034 to 3.768 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.06667 | 0.04288 | P > 0.05 | ns |
| 1 | -2.833 | 1.823 | P > 0.05 | ns |
| 2 | -1.133 | 0.729 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 10.37 | 0.5201 |
| Time | 25.97 | 0.2295 |
| Treatment | 1.58 | 0.2611 |
| Subjects (matching) | 3.6893 | 0.9687 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 3.741 | 1.871 | 0.7103 |
| Time | 2 | 9.37 | 4.685 | 1.779 |
| Treatment | 1 | 0.5689 | 0.5689 | 1.71 |
| Subjects (matching) | 4 | 1.331 | 0.3328 | 0.1264 |
| Residual | 8 | 21.07 | 2.634 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.033 | 7 | 0.9667 | -2.550 to 4.484 |
| 1 | 7.133 | 6.2 | -0.9333 | -4.450 to 2.584 |
| 2 | 7.6 | 8.633 | 1.033 | -2.484 to 4.550 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.9667 | 0.8665 | P > 0.05 | ns |
| 1 | -0.9333 | 0.8367 | P > 0.05 | ns |
| 2 | 1.033 | 0.9263 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 12.06 | 0.1439 |
| Time | 50.13 | 0.006 |
| Treatment | 8.91 | 0.1257 |
| Subjects (matching) | 9.5562 | 0.4661 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 9.101 | 4.551 | 2.494 |
| Time | 2 | 37.83 | 18.92 | 10.37 |
| Treatment | 1 | 6.722 | 6.722 | 3.729 |
| Subjects (matching) | 4 | 7.211 | 1.803 | 0.9881 |
| Residual | 8 | 14.6 | 1.824 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 7.667 | 0.2 | -3.270 to 3.670 |
| 1 | 7.8 | 11.03 | 3.233 | -0.2367 to 6.703 |
| 2 | 11 | 11.23 | 0.2333 | -3.237 to 3.703 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2 | 0.1817 | P > 0.05 | ns |
| 1 | 3.233 | 2.938 | P < 0.05 | * |
| 2 | 0.2333 | 0.212 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 7.61 | 0.1384 |
| Time | 72.4 | 0.0004 |
| Treatment | 1.24 | 0.4428 |
| Subjects (matching) | 6.8482 | 0.3996 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.308 | 3.154 | 2.558 |
| Time | 2 | 60 | 30 | 24.33 |
| Treatment | 1 | 1.027 | 1.027 | 0.724 |
| Subjects (matching) | 4 | 5.676 | 1.419 | 1.151 |
| Residual | 8 | 9.864 | 1.233 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.133 | 9 | -0.1333 | -3.063 to 2.796 |
| 1 | 9.6 | 11.73 | 2.133 | -0.7960 to 5.063 |
| 2 | 13.77 | 13.2 | -0.5667 | -3.496 to 2.363 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1333 | 0.1435 | P > 0.05 | ns |
| 1 | 2.133 | 2.296 | P > 0.05 | ns |
| 2 | -0.5667 | 0.6099 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 15.91 | 0.0569 |
| Time | 22.91 | 0.0253 |
| Treatment | 41.98 | 0.0029 |
| Subjects (matching) | 4.0177 | 0.7183 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 16.99 | 8.494 | 4.192 |
| Time | 2 | 24.45 | 12.23 | 6.034 |
| Treatment | 1 | 44.81 | 44.81 | 41.79 |
| Subjects (matching) | 4 | 4.289 | 1.072 | 0.5291 |
| Residual | 8 | 16.21 | 2.026 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 17.37 | 15.47 | -1.9 | -5.265 to 1.465 |
| 1 | 16.57 | 10.67 | -5.9 | -9.265 to -2.536 |
| 2 | 16.33 | 14.67 | -1.667 | -5.031 to 1.698 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.9 | 1.78 | P > 0.05 | ns |
| 1 | -5.9 | 5.529 | P<0.001 | *** |
| 2 | -1.667 | 1.562 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-11M Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 50.28 | 0.0002 |
| Time | 30.39 | 0.0013 |
| Treatment | 9.89 | 0.0145 |
| Subjects (matching) | 2.3226 | 0.6416 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | ** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 49.21 | 24.61 | 28.23 |
| Time | 2 | 29.74 | 14.87 | 17.06 |
| Treatment | 1 | 9.68 | 9.68 | 17.03 |
| Subjects (matching) | 4 | 2.273 | 0.5683 | 0.652 |
| Residual | 8 | 6.973 | 0.8717 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.13 | 9.633 | -1.5 | -3.760 to 0.7596 |
| 1 | 15.8 | 10.3 | -5.5 | -7.760 to -3.240 |
| 2 | 8.967 | 11.57 | 2.6 | 0.3404 to 4.860 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.5 | 2.093 | P > 0.05 | ns |
| 1 | -5.5 | 7.674 | P<0.001 | *** |
| 2 | 2.6 | 3.628 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-12M Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 27.78 | 0.03 |
| Time | 26.78 | 0.0326 |
| Treatment | 4.66 | 0.399 |
| Subjects (matching) | 20.9796 | 0.1699 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 27.4 | 13.7 | 5.614 |
| Time | 2 | 26.41 | 13.21 | 5.411 |
| Treatment | 1 | 4.601 | 4.601 | 0.8894 |
| Subjects (matching) | 4 | 20.69 | 5.173 | 2.12 |
| Residual | 8 | 19.52 | 2.44 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.83 | 11.5 | 0.6667 | -4.046 to 5.379 |
| 1 | 11.97 | 12.77 | 0.8 | -3.912 to 5.512 |
| 2 | 16.37 | 11.87 | -4.5 | -9.212 to 0.2123 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6667 | 0.446 | P > 0.05 | ns |
| 1 | 0.8 | 0.5352 | P > 0.05 | ns |
| 2 | -4.5 | 3.011 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-12M Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.72 | 0.3225 |
| Time | 1.62 | 0.7022 |
| Treatment | 47.43 | 0.0591 |
| Subjects (matching) | 27.732 | 0.0773 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 6.948 | 3.474 | 1.308 |
| Time | 2 | 1.963 | 0.9817 | 0.3696 |
| Treatment | 1 | 57.6 | 57.6 | 6.842 |
| Subjects (matching) | 4 | 33.68 | 8.419 | 3.17 |
| Residual | 8 | 21.25 | 2.656 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.13 | 13.3 | -1.833 | -7.341 to 3.674 |
| 1 | 17.03 | 12.77 | -4.267 | -9.774 to 1.241 |
| 2 | 16.5 | 11.87 | -4.633 | -10.14 to 0.8739 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.833 | 1.05 | P > 0.05 | ns |
| 1 | -4.267 | 2.442 | P > 0.05 | ns |
| 2 | -4.633 | 2.652 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 6.36 | 0.5867 |
| Time | 13.03 | 0.3586 |
| Treatment | 4.99 | 0.4679 |
| Subjects (matching) | 31.0654 | 0.3186 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 30.05 | 15.02 | 0.5704 |
| Time | 2 | 61.58 | 30.79 | 1.169 |
| Treatment | 1 | 23.58 | 23.58 | 0.6421 |
| Subjects (matching) | 4 | 146.9 | 36.72 | 1.394 |
| Residual | 8 | 210.7 | 26.34 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.033 | 6.267 | 0.2333 | -13.82 to 14.28 |
| 1 | 7.133 | 7.833 | 0.7 | -13.35 to 14.75 |
| 2 | 7.6 | 13.53 | 5.933 | -8.118 to 19.98 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2333 | 0.05235 | P > 0.05 | ns |
| 1 | 0.7 | 0.1571 | P > 0.05 | ns |
| 2 | 5.933 | 1.331 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 5.41 | 0.5362 |
| Time | 21.62 | 0.1275 |
| Treatment | 6.77 | 0.4234 |
| Subjects (matching) | 34.1127 | 0.169 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 32.14 | 16.07 | 0.6743 |
| Time | 2 | 128.4 | 64.21 | 2.694 |
| Treatment | 1 | 40.2 | 40.2 | 0.7935 |
| Subjects (matching) | 4 | 202.6 | 50.66 | 2.126 |
| Residual | 8 | 190.6 | 23.83 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 6.7 | -0.7667 | -15.50 to 13.97 |
| 1 | 7.8 | 12.3 | 4.5 | -10.24 to 19.24 |
| 2 | 11 | 16.23 | 5.233 | -9.503 to 19.97 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.7667 | 0.164 | P > 0.05 | ns |
| 1 | 4.5 | 0.9627 | P > 0.05 | ns |
| 2 | 5.233 | 1.12 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | 10-12M Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 36.26 | 0.0393 |
| Time | 26.14 | 0.077 |
| Treatment | 3.14 | 0.2009 |
| Subjects (matching) | 5.3758 | 0.8241 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 32.3 | 16.15 | 4.986 |
| Time | 2 | 23.28 | 11.64 | 3.595 |
| Treatment | 1 | 2.801 | 2.801 | 2.339 |
| Subjects (matching) | 4 | 4.789 | 1.197 | 0.3696 |
| Residual | 8 | 25.91 | 3.239 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.133 | 8.7 | -0.4333 | -4.551 to 3.684 |
| 1 | 9.6 | 11.9 | 2.3 | -1.817 to 6.417 |
| 2 | 13.77 | 9.533 | -4.233 | -8.351 to -0.1160 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4333 | 0.3318 | P > 0.05 | ns |
| 1 | 2.3 | 1.761 | P > 0.05 | ns |
| 2 | -4.233 | 3.242 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | 10-12M Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 2.82 | 0.4019 |
| Time | 11.23 | 0.06 |
| Treatment | 65.48 | 0.0062 |
| Subjects (matching) | 9.4597 | 0.2384 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 3.488 | 1.744 | 1.024 |
| Time | 2 | 13.9 | 6.952 | 4.081 |
| Treatment | 1 | 81.07 | 81.07 | 27.69 |
| Subjects (matching) | 4 | 11.71 | 2.928 | 1.719 |
| Residual | 8 | 13.63 | 1.704 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Saline vs. glucan

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 17.37 | 14.37 | -3 | -6.741 to 0.7406 |
| 1 | 16.57 | 11.73 | -4.833 | -8.574 to -1.093 |
| 2 | 16.33 | 11.43 | -4.9 | -8.641 to -1.159 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3 | 2.528 | P > 0.05 | ns |
| 1 | -4.833 | 4.074 | P<0.01 | ** |
| 2 | -4.9 | 4.13 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | 10-12M Dectin-1 |
| Two-way RM ANOVA | *Matching by cols* |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 9.24 | 0.0468 |
| Time | 48.62 | 0.0004 |
| Treatment | 25.78 | 0.0244 |
| Subjects (matching) | 8.3206 | 0.1769 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | *** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 2 | 13.56 | 6.782 | 4.598 |
| Time | 2 | 71.36 | 35.68 | 24.19 |
| Treatment | 1 | 37.85 | 37.85 | 12.39 |
| Subjects (matching) | 4 | 12.21 | 3.053 | 2.07 |
| Residual | 8 | 11.8 | 1.475 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

*Saline vs. glucan*

| Treatment | Saline | glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 11.13 | 8.467 | -2.667 | -6.308 to 0.9747 |
| 1 | 15.8 | 10.67 | -5.133 | -8.775 to -1.492 |
| 2 | 8.967 | 8.067 | -0.9 | -4.541 to 2.741 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.667 | 2.309 | P > 0.05 | ns |
| 1 | -5.133 | 4.444 | P<0.01 | ** |
| 2 | -0.9 | 0.7792 | P > 0.05 | ns |

## APPENDIX IV – ANOVA TABLES NEO A + GLUCAN

| | | |
|---|---|---|
| Table Analyzed | Bmp2 10-9 | |
| Two-way RM ANOVA | Matching by cols | |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 9.8 | 0.4539 |
| Time | 16.09 | 0.0758 |
| Treatment | 28.23 | 0.0468 |
| Subjects (matching) | 15.9071 | 0.4356 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 39.03 | 9.756 | 0.981 |
| Time | 2 | 64.09 | 32.05 | 3.222 |
| Treatment | 2 | 112.4 | 56.2 | 5.324 |
| Subjects (matching) | 6 | 63.34 | 10.56 | 1.062 |
| Residual | 12 | 119.3 | 9.945 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + Glucan vs. Neo A

| Treatment | Neo A + Glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.2 | -1.533 | -3.733 | -11.44 to 3.973 |
| 1 | 2.533 | 4.5 | 1.967 | -5.740 to 9.673 |
| 2 | 4.767 | 3.067 | -1.7 | -9.407 to 6.007 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.733 | 1.435 | P > 0.05 | ns |
| 1 | 1.967 | 0.7561 | P > 0.05 | ns |
| 2 | -1.7 | 0.6535 | P > 0.05 | ns |

Neo A + Glucan vs. Glucan

| Treatment | Neo A + Glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.2 | -3.067 | -5.267 | -12.97 to 2.440 |
| 1 | 2.533 | -2.833 | -5.367 | -13.07 to 2.340 |
| 2 | 4.767 | 1.033 | -3.733 | -11.44 to 3.973 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -5.267 | 2.025 | P > 0.05 | ns |
| 1 | -5.367 | 2.063 | P > 0.05 | ns |
| 2 | -3.733 | 1.435 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Hspb1 10-9 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 15.62 | 0.4242 |
| Time | 4.1 | 0.5916 |
| Treatment | 22.46 | 0.0493 |
| Subjects (matching) | 13.0039 | 0.7398 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 32.16 | 8.039 | 1.046 |
| Time | 2 | 8.436 | 4.218 | 0.5485 |
| Treatment | 2 | 46.25 | 23.12 | 5.182 |
| Subjects (matching) | 6 | 26.77 | 4.462 | 0.5803 |
| Residual | 12 | 92.27 | 7.689 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + Glucan vs. Neo A

| Treatment | Neo A + Glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.833 | 1.367 | -2.467 | -9.078 to 4.145 |
| 1 | 2.533 | 5.9 | 3.367 | -3.245 to 9.978 |
| 2 | 4.767 | 3.067 | -1.7 | -8.311 to 4.911 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.467 | 1.175 | P > 0.05 | ns |
| 1 | 3.367 | 1.603 | P > 0.05 | ns |
| 2 | -1.7 | 0.8096 | P > 0.05 | ns |

Neo A + Glucan vs. Glucan

| Treatment | Neo A + Glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.833 | 0.5667 | -3.267 | -9.878 to 3.345 |
| 1 | 2.533 | 1.4 | -1.133 | -7.745 to 5.478 |
| 2 | 4.767 | 0.4667 | -4.3 | -10.91 to 2.311 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.267 | 1.556 | P > 0.05 | ns |
| 1 | -1.133 | 0.5397 | P > 0.05 | ns |
| 2 | -4.3 | 2.048 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Icam1 10-9 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 7.94 | 0.0977 |
| Time | 3.11 | 0.1827 |
| Treatment | 76.98 | P<0.0001 |
| Subjects (matching) | 2.4612 | 0.7844 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 69.66 | 17.41 | 2.505 |
| Time | 2 | 27.32 | 13.66 | 1.965 |
| Treatment | 2 | 675.4 | 337.7 | 93.83 |
| Subjects (matching) | 6 | 21.59 | 3.599 | 0.5177 |
| Residual | 12 | 83.41 | 6.951 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12.37 | 10.33 | -2.033 | -7.876 to 3.809 |
| 1 | 12.3 | 11.33 | -0.9667 | -6.809 to 4.876 |
| 2 | 11.93 | 4.233 | -7.7 | -13.54 to -1.857 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.033 | 1.031 | P > 0.05 | ns |
| 1 | -0.9667 | 0.4902 | P > 0.05 | ns |
| 2 | -7.7 | 3.904 | P<0.01 | ** |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12.37 | -1.067 | -13.43 | -19.28 to -7.591 |
| 1 | 12.3 | 0.8667 | -11.43 | -17.28 to -5.591 |
| 2 | 11.93 | 1 | -10.93 | -16.78 to -5.091 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -13.43 | 6.812 | P<0.001 | *** |
| 1 | -11.43 | 5.798 | P<0.001 | *** |
| 2 | -10.93 | 5.544 | P<0.001 | *** |

| | |
|---|---|
| Table Analyzed | Vegfa 10-9 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 16.7 | 0.0377 |
| Time | 12.5 | 0.0214 |
| Treatment | 47.8 | 0.0041 |
| Subjects (matching) | 9.0841 | 0.3261 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 90.3 | 22.57 | 3.599 |
| Time | 2 | 67.58 | 33.79 | 5.388 |
| Treatment | 2 | 258.4 | 129.2 | 15.79 |
| Subjects (matching) | 6 | 49.12 | 8.186 | 1.305 |
| Residual | 12 | 75.26 | 6.272 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.533 | 7.2 | 3.667 | -2.692 to 10.03 |
| 1 | 8.433 | 11.37 | 2.933 | -3.426 to 9.292 |
| 2 | 11.57 | 6.4 | -5.167 | -11.53 to 1.192 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.667 | 1.708 | P > 0.05 | ns |
| 1 | 2.933 | 1.367 | P > 0.05 | ns |
| 2 | -5.167 | 2.407 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.533 | 0.2667 | -3.267 | -9.626 to 3.092 |
| 1 | 8.433 | 0.9 | -7.533 | -13.89 to -1.174 |
| 2 | 11.57 | 3.433 | -8.133 | -14.49 to -1.774 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.267 | 1.522 | P > 0.05 | ns |
| 1 | -7.533 | 3.51 | P<0.01 | ** |
| 2 | -8.133 | 3.789 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | Cdknlb 10-9 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 25.44 | 0.0339 |
| Time | 2.98 | 0.4424 |
| Treatment | 44.19 | 0.0025 |
| Subjects (matching) | 6.9252 | 0.6715 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 76.9 | 19.23 | 3.73 |
| Time | 2 | 9.007 | 4.503 | 0.8736 |
| Treatment | 2 | 133.5 | 66.77 | 19.14 |
| Subjects (matching) | 6 | 20.93 | 3.489 | 0.6768 |
| Residual | 12 | 61.86 | 5.155 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 5.467 | 6.333 | 0.8667 | -4.321 to 6.055 |
| 1 | 7.2 | 7.567 | 0.3667 | -4.821 to 5.555 |
| 2 | 7.667 | 3.067 | -4.6 | -9.788 to 0.5879 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.8667 | 0.4949 | P > 0.05 | ns |
| 1 | 0.3667 | 0.2094 | P > 0.05 | ns |
| 2 | -4.6 | 2.627 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 5.467 | -0.2 | -5.667 | -10.85 to -0.4788 |
| 1 | 7.2 | 0.2333 | -6.967 | -12.15 to -1.779 |
| 2 | 7.667 | 4.767 | -2.9 | -8.088 to 2.288 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -5.667 | 3.236 | P < 0.05 | * |
| 1 | -6.967 | 3.979 | P<0.01 | ** |
| 2 | -2.9 | 1.656 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Cd5 10-9 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 13.08 | 0.5407 |
| Time | 6.57 | 0.4649 |
| Treatment | 21.24 | 0.0384 |
| Subjects (matching) | 10.8128 | 0.8332 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 21.96 | 5.49 | 0.8129 |
| Time | 2 | 11.03 | 5.517 | 0.8169 |
| Treatment | 2 | 35.65 | 17.82 | 5.893 |
| Subjects (matching) | 6 | 18.15 | 3.024 | 0.4478 |
| Residual | 12 | 81.04 | 6.753 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.433 | 0.4333 | -4 | -9.679 to 1.679 |
| 1 | 2.533 | 3.467 | 0.9333 | -4.745 to 6.612 |
| 2 | 5.167 | 3.067 | -2.1 | -7.779 to 3.579 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4 | 2.087 | P > 0.05 | ns |
| 1 | 0.9333 | 0.487 | P > 0.05 | ns |
| 2 | -2.1 | 1.096 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.433 | 1.467 | -2.967 | -8.645 to 2.712 |
| 1 | 2.533 | 0.2 | -2.333 | -8.012 to 3.345 |
| 2 | 5.167 | 2.1 | -3.067 | -8.745 to 2.612 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.967 | 1.548 | P > 0.05 | ns |
| 1 | -2.333 | 1.217 | P > 0.05 | ns |
| 2 | -3.067 | 1.6 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Dectin-1 10-9 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 27.89 | 0.0539 |
| Time | 28.98 | 0.0117 |
| Treatment | 11.8 | 0.0257 |
| Subjects (matching) | 4.9451 | 0.8812 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 81.49 | 20.37 | 3.171 |
| Time | 2 | 84.67 | 42.34 | 6.591 |
| Treatment | 2 | 34.49 | 17.25 | 7.161 |
| Subjects (matching) | 6 | 14.45 | 2.408 | 0.3749 |
| Residual | 12 | 77.08 | 6.424 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2 | 2.2 | 0.2 | -5.255 to 5.655 |
| 1 | 4.767 | 2.767 | -2 | -7.455 to 3.455 |
| 2 | 10.43 | 5.633 | -4.8 | -10.26 to 0.6551 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2 | 0.1086 | P > 0.05 | ns |
| 1 | -2 | 1.086 | P > 0.05 | ns |
| 2 | -4.8 | 2.607 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2 | 1.3 | -0.7 | -6.155 to 4.755 |
| 1 | 4.767 | 5.9 | 1.133 | -4.322 to 6.588 |
| 2 | 10.43 | 2.333 | -8.1 | -13.56 to -2.645 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.7 | 0.3802 | P > 0.05 | ns |
| 1 | 1.133 | 0.6155 | P > 0.05 | ns |
| 2 | -8.1 | 4.399 | P<0.01 | ** |

| | |
|---|---|
| Table Analyzed | Bmp2 10-10 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 15.39 | 0.0464 |
| Time | 32.54 | 0.0007 |
| Treatment | 29.89 | 0.0105 |
| Subjects (matching) | 8.3806 | 0.3632 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | *** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 47.16 | 11.79 | 3.348 |
| Time | 2 | 99.69 | 49.84 | 14.15 |
| Treatment | 2 | 91.58 | 45.79 | 10.7 |
| Subjects (matching) | 6 | 25.68 | 4.279 | 1.215 |
| Residual | 12 | 42.26 | 3.522 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + Glucan vs. Neo A

| Treatment | Neo A + Glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.6333 | 0.4333 | 1.067 | -3.633 to 5.766 |
| 1 | 2.467 | 7.867 | 5.4 | 0.7003 to 10.10 |
| 2 | 5.267 | 5.5 | 0.2333 | -4.466 to 4.933 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.067 | 0.6724 | P > 0.05 | ns |
| 1 | 5.4 | 3.404 | P<0.01 | ** |
| 2 | 0.2333 | 0.1471 | P > 0.05 | ns |

Neo A + Glucan vs. Glucan

| Treatment | Neo A + Glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.6333 | -0.8 | -0.1667 | -4.866 to 4.533 |
| 1 | 2.467 | -0.3333 | -2.8 | -7.500 to 1.900 |
| 2 | 5.267 | 1.4 | -3.867 | -8.566 to 0.8331 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1667 | 0.1051 | P > 0.05 | ns |
| 1 | -2.8 | 1.765 | P > 0.05 | ns |
| 2 | -3.867 | 2.438 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Hspb1 10-10 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 17.25 | 0.0795 |
| Time | 17.37 | 0.0202 |
| Treatment | 42.46 | 0.0006 |
| Subjects (matching) | 3.9672 | 0.8529 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 31.06 | 7.764 | 2.73 |
| Time | 2 | 31.29 | 15.64 | 5.5 |
| Treatment | 2 | 76.47 | 38.23 | 32.11 |
| Subjects (matching) | 6 | 7.144 | 1.191 | 0.4187 |
| Residual | 12 | 34.13 | 2.844 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + Glucan vs. Neo A

| Treatment | Neo A + Glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.267 | 2.133 | -0.1333 | -4.026 to 3.760 |
| 1 | 2.467 | 7.867 | 5.4 | 1.507 to 9.293 |
| 2 | 4.633 | 5.5 | 0.8667 | -3.026 to 4.760 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1333 | 0.1078 | P > 0.05 | ns |
| 1 | 5.4 | 4.368 | P<0.01 | ** |
| 2 | 0.8667 | 0.701 | P > 0.05 | ns |

Neo A + Glucan vs. Glucan

| Treatment | Neo A + Glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.267 | 0.3667 | -1.9 | -5.793 to 1.993 |
| 1 | 2.467 | 1.233 | -1.233 | -5.126 to 2.660 |
| 2 | 4.633 | 1.533 | -3.1 | -6.993 to 0.7929 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.9 | 1.537 | P > 0.05 | ns |
| 1 | -1.233 | 0.9975 | P > 0.05 | ns |
| 2 | -3.1 | 2.507 | P > 0.05 | ns |

| | | | | | |
|---|---|---|---|---|---|
| Table Analyzed | Icam1 10-10 | | | | |
| Two-way RM ANOVA | Matching by cols | | | | |
| Source of Variation | % of total variation | P value | | | |
| Interaction | 1.92 | 0.3172 | | | |
| Time | 0.86 | 0.3384 | | | |
| Treatment | 90.6 | P<0.0001 | | | |
| Subjects (matching) | 2.2509 | 0.4515 | | | |
| Source of Variation | P value summary | Significant? | | | |
| Interaction | ns | No | | | |
| Time | ns | No | | | |
| Treatment | *** | Yes | | | |
| Subjects (matching) | ns | No | | | |
| Source of Variation | Df | Sum-of-squares | Mean square | F | |
| Interaction | 4 | 15.92 | 3.979 | 1.322 | |
| Time | 2 | 7.15 | 3.575 | 1.187 | |
| Treatment | 2 | 749.7 | 374.9 | 120.7 | |
| Subjects (matching) | 6 | 18.63 | 3.104 | 1.031 | |
| Residual | 12 | 36.13 | 3.011 | | |
| Number of missing values | 0 | | | | |
| Bonferroni posttests | | | | | |
| Neo A + glucan vs. Neo A | | | | | |
| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. | |
| 0.5 | 10.3 | 12.77 | 2.467 | -1.752 to 6.686 | |
| 1 | 11.87 | 10.7 | -1.167 | -5.386 to 3.052 | |
| 2 | 12.47 | 11.5 | -0.9667 | -5.186 to 3.252 | |
| Treatment | Difference | t | P value | Summary | |
| 0.5 | 2.467 | 1.732 | P > 0.05 | ns | |
| 1 | -1.167 | 0.8193 | P > 0.05 | ns | |
| 2 | -0.9667 | 0.6788 | P > 0.05 | ns | |
| Neo A + glucan vs. Glucan | | | | | |
| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. | |
| 0.5 | 10.3 | -0.4 | -10.7 | -14.92 to -6.481 | |
| 1 | 11.87 | -0.1667 | -12.03 | -16.25 to -7.814 | |
| 2 | 12.47 | 1.833 | -10.63 | -14.85 to -6.414 | |
| Treatment | Difference | t | P value | Summary | |
| 0.5 | -10.7 | 7.514 | P<0.001 | *** | |
| 1 | -12.03 | 8.45 | P<0.001 | *** | |
| 2 | -10.63 | 7.467 | P<0.001 | *** | |

| | | | | | |
|---|---|---|---|---|---|
| Table Analyzed | Vegfa 10-10 | | | | |
| Two-way RM ANOVA | Matching by cols | | | | |
| Source of Variation | % of total variation | P value | | | |
| *Interaction* | 1.2 | 0.7356 | | | |
| Time | 12.23 | 0.0025 | | | |
| Treatment | 75.64 | 0.0001 | | | |
| Subjects (matching) | 3.7668 | 0.4404 | | | |
| Source of Variation | P value summary | Significant? | | | |
| Interaction | ns | No | | | |
| Time | ** | Yes | | | |
| Treatment | *** | Yes | | | |
| Subjects (matching) | ns | No | | | |
| Source of Variation | Df | Sum-of-squares | Mean square | F | |
| Interaction | 4 | 8.333 | 2.083 | 0.5013 | |
| Time | 2 | 85.21 | 42.61 | 10.25 | |
| Treatment | 2 | 526.9 | 263.5 | 60.25 | |
| Subjects (matching) | 6 | 26.24 | 4.373 | 1.052 | |
| Residual | 12 | 49.87 | 4.156 | | |
| Number of missing values | 0 | | | | |
| Bonferroni posttests | | | | | |
| Neo A + glucan vs. Neo A | | | | | |
| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. | |
| 0.5 | 7.467 | 8.367 | 0.9 | -4.074 to 5.874 | |
| 1 | 9.533 | 11.33 | 1.8 | -3.174 to 6.774 | |
| 2 | 12.63 | 13.6 | 0.9667 | -4.008 to 5.941 | |
| Treatment | Difference | t | P value | Summary | |
| 0.5 | 0.9 | 0.5361 | P > 0.05 | ns | |
| 1 | 1.8 | 1.072 | P > 0.05 | ns | |
| 2 | 0.9667 | 0.5758 | P > 0.05 | ns | |
| Neo A + glucan vs. Glucan | | | | | |
| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. | |
| 0.5 | 7.467 | 0.1667 | -7.3 | -12.27 to -2.326 | |
| 1 | 9.533 | 0.6 | -8.933 | -13.91 to -3.959 | |
| 2 | 12.63 | 2.767 | -9.867 | -14.84 to -4.892 | |
| Treatment | Difference | t | P value | Summary | |
| 0.5 | -7.3 | 4.348 | P<0.01 | ** | |
| 1 | -8.933 | 5.321 | P<0.001 | *** | |
| 2 | -9.867 | 5.877 | P<0.001 | *** | |

| | |
|---|---|
| Table Analyzed | Cdknlb 10-10 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 4.79 | 0.4399 |
| Time | 8.56 | 0.0593 |
| Treatment | 67.36 | 0.0003 |
| Subjects (matching) | 5.0644 | 0.6471 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ns | No |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 22.82 | 5.706 | 1.011 |
| Time | 2 | 40.74 | 20.37 | 3.609 |
| Treatment | 2 | 320.7 | 160.4 | 39.9 |
| Subjects (matching) | 6 | 24.11 | 4.019 | 0.712 |
| Residual | 12 | 67.73 | 5.644 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.667 | 7.4 | 0.7333 | -4.731 to 6.198 |
| 1 | 9.267 | 9.767 | 0.5 | -4.964 to 5.964 |
| 2 | 9.633 | 8.467 | -1.167 | -6.631 to 4.298 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7333 | 0.3976 | P > 0.05 | ns |
| 1 | 0.5 | 0.2711 | P > 0.05 | ns |
| 2 | -1.167 | 0.6326 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.667 | -0.7 | -7.367 | -12.83 to -1.902 |
| 1 | 9.267 | 0.2333 | -9.033 | -14.50 to -3.569 |
| 2 | 9.633 | 4.133 | -5.5 | -10.96 to -0.03559 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -7.367 | 3.994 | P<0.01 | ** |
| 1 | -9.033 | 4.898 | P<0.001 | *** |
| 2 | -5.5 | 2.982 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | Cd5 10-10 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| *Interaction* | 22.03 | 0.0636 |
| Time | 18.23 | 0.0274 |
| Treatment | 29.52 | 0.0098 |
| Subjects (matching) | 8.0284 | 0.639 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 47.71 | 11.93 | 2.98 |
| Time | 2 | 39.47 | 19.74 | 4.93 |
| Treatment | 2 | 63.93 | 31.97 | 11.03 |
| Subjects (matching) | 6 | 17.38 | 2.897 | 0.7238 |
| Residual | 12 | 48.04 | 4.003 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.767 | 2.433 | 0.6667 | -3.945 to 5.278 |
| 1 | 4.867 | 7.867 | 3 | -1.612 to 7.612 |
| 2 | 5.533 | 6.667 | 1.133 | -3.478 to 5.745 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6667 | 0.4283 | P > 0.05 | ns |
| 1 | 3 | 1.927 | P > 0.05 | ns |
| 2 | 1.133 | 0.7281 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.767 | 2.467 | 0.7 | -3.912 to 5.312 |
| 1 | 4.867 | 0.1667 | -4.7 | -9.312 to -0.08824 |
| 2 | 5.533 | 3.067 | -2.467 | -7.078 to 2.145 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7 | 0.4497 | P > 0.05 | ns |
| 1 | -4.7 | 3.019 | P < 0.05 | * |
| 2 | -2.467 | 1.585 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Dectin-1 10-10 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 33.4 | 0.0067 |
| Time | 36.71 | 0.0009 |
| Treatment | 7.45 | 0.0848 |
| Subjects (matching) | 5.8341 | 0.6537 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 4 | 118.9 | 29.73 | 6.032 |
| Time | 2 | 130.7 | 65.34 | 13.26 |
| Treatment | 2 | 26.52 | 13.26 | 3.83 |
| Subjects (matching) | 6 | 20.77 | 3.462 | 0.7024 |
| Residual | 12 | 59.14 | 4.929 | |

| | |
|---|---|
| Number of missing values | 0 |

Bonferroni posttests

Neo A + glucan vs. Neo A

| Treatment | Neo A + glucan | Neo A | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.7 | 3.867 | 2.167 | -2.930 to 7.264 |
| 1 | 4.267 | 3.933 | -0.3333 | -5.430 to 4.764 |
| 2 | 11.23 | 9.733 | -1.5 | -6.597 to 3.597 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.167 | 1.259 | P > 0.05 | ns |
| 1 | -0.3333 | 0.1938 | P > 0.05 | ns |
| 2 | -1.5 | 0.8719 | P > 0.05 | ns |

Neo A + glucan vs. Glucan

| Treatment | Neo A + glucan | Glucan | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.7 | 1.933 | 0.2333 | -4.864 to 5.330 |
| 1 | 4.267 | 6.467 | 2.2 | -2.897 to 7.297 |
| 2 | 11.23 | 2.667 | -8.567 | -13.66 to -3.470 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2333 | 0.1356 | P > 0.05 | ns |
| 1 | 2.2 | 1.279 | P > 0.05 | ns |
| 2 | -8.567 | 4.979 | P<0.001 | *** |

APPENDIX V – ANOVA TABLES Neo A Dose Dependence

| | |
|---|---|
| Table Analyzed | Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 17.16 | 0.0506 |
| Time | 37.9 | P<0.0001 |
| Treatment | 14.82 | 0.0747 |
| Subjects (matching) | 12.5238 | 0.24 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 126.2 | 15.77 | 2.439 |
| Time | 2 | 278.6 | 139.3 | 21.54 |
| Treatment | 4 | 109 | 27.25 | 2.959 |
| Subjects (matching) | 10 | 92.08 | 9.208 | 1.424 |
| Residual | 20 | 129.3 | 6.467 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.633 | -1.533 | -5.167 | -12.83 to 2.496 |
| 1 | 11.33 | 4.5 | -6.833 | -14.50 to 0.8291 |
| 2 | 2.1 | 3.067 | 0.9667 | -6.696 to 8.629 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -5.167 | 2.329 | P > 0.05 | ns |
| 1 | -6.833 | 3.081 | P < 0.05 | * |
| 2 | 0.9667 | 0.4358 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.633 | 0.4333 | -3.2 | -10.86 to 4.462 |
| 1 | 11.33 | 7.867 | -3.467 | -11.13 to 4.196 |
| 2 | 2.1 | 5.5 | 3.4 | -4.262 to 11.06 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.2 | 1.443 | P > 0.05 | ns |
| 1 | -3.467 | 1.563 | P > 0.05 | ns |
| 2 | 3.4 | 1.533 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.633 | -0.5333 | -4.167 | -11.83 to 3.496 |
| 1 | 11.33 | 7.933 | -3.4 | -11.06 to 4.262 |
| 2 | 2.1 | 4.667 | 2.567 | -5.096 to 10.23 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.167 | 1.878 | P > 0.05 | ns |
| 1 | -3.4 | 1.533 | P > 0.05 | ns |
| 2 | 2.567 | 1.157 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.633 | 0.9 | -2.733 | -10.40 to 4.929 |
| 1 | 11.33 | 1.733 | -9.6 | -17.26 to -1.938 |
| 2 | 2.1 | 2.133 | 0.03333 | -7.629 to 7.696 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.733 | 1.232 | P > 0.05 | ns |
| 1 | -9.6 | 4.328 | P<0.001 | *** |
| 2 | 0.03333 | 0.01503 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.533 | 0.4333 | 1.967 | -5.696 to 9.629 |
| 1 | 4.5 | 7.867 | 3.367 | -4.296 to 11.03 |
| 2 | 3.067 | 5.5 | 2.433 | -5.229 to 10.10 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.967 | 0.8866 | P > 0.05 | ns |
| 1 | 3.367 | 1.518 | P > 0.05 | ns |
| 2 | 2.433 | 1.097 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.533 | -0.5333 | 1 | -6.662 to 8.662 |
| 1 | 4.5 | 7.933 | 3.433 | -4.229 to 11.10 |
| 2 | 3.067 | 4.667 | 1.6 | -6.062 to 9.262 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1 | 0.4508 | P > 0.05 | ns |
| 1 | 3.433 | 1.548 | P > 0.05 | ns |
| 2 | 1.6 | 0.7213 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.533 | 0.9 | 2.433 | -5.229 to 10.10 |
| 1 | 4.5 | 1.733 | -2.767 | -10.43 to 4.896 |
| 2 | 3.067 | 2.133 | -0.9333 | -8.596 to 6.729 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.433 | 1.097 | P > 0.05 | ns |
| 1 | -2.767 | 1.247 | P > 0.05 | ns |
| 2 | -0.9333 | 0.4208 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.4333 | -0.5333 | -0.9667 | -8.629 to 6.696 |
| 1 | 7.867 | 7.933 | 0.06667 | -7.596 to 7.729 |
| 2 | 5.5 | 4.667 | -0.8333 | -8.496 to 6.829 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9667 | 0.4358 | P > 0.05 | ns |
| 1 | 0.06667 | 0.03005 | P > 0.05 | ns |
| 2 | -0.8333 | 0.3757 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.4333 | 0.9 | 0.4667 | -7.196 to 8.129 |
| 1 | 7.867 | 1.733 | -6.133 | -13.80 to 1.529 |
| 2 | 5.5 | 2.133 | -3.367 | -11.03 to 4.296 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.4667 | 0.2104 | P > 0.05 | ns |
| 1 | -6.133 | 2.765 | P < 0.05 | * |
| 2 | -3.367 | 1.518 | P > 0.05 | ns |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.5333 | 0.9 | 1.433 | -6.229 to 9.096 |
| 1 | 7.933 | 1.733 | -6.2 | -13.86 to 1.462 |
| 2 | 4.667 | 2.133 | -2.533 | -10.20 to 5.129 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.433 | 0.6462 | P > 0.05 | ns |
| 1 | -6.2 | 2.795 | P < 0.05 | * |
| 2 | -2.533 | 1.142 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 7.74 | 0.7098 |
| Time | 44.06 | P<0.0001 |
| Treatment | 10.46 | 0.0775 |
| Subjects (matching) | 8.9725 | 0.7767 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 27.85 | 3.481 | 0.6724 |
| Time | 2 | 158.5 | 79.24 | 15.31 |
| Treatment | 4 | 37.61 | 9.403 | 2.913 |
| Subjects (matching) | 10 | 32.28 | 3.228 | 0.6236 |
| Residual | 20 | 103.5 | 5.176 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.067 | 1.367 | 0.3 | -5.701 to 6.301 |
| 1 | 5.633 | 5.9 | 0.2667 | -5.734 to 6.268 |
| 2 | 3.233 | 3.067 | -0.1667 | -6.168 to 5.834 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.3 | 0.1727 | P > 0.05 | ns |
| 1 | 0.2667 | 0.1535 | P > 0.05 | ns |
| 2 | -0.1667 | 0.09594 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.067 | 2.133 | 1.067 | -4.934 to 7.068 |
| 1 | 5.633 | 7.867 | 2.233 | -3.768 to 8.234 |
| 2 | 3.233 | 5.5 | 2.267 | -3.734 to 8.268 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.067 | 0.614 | P > 0.05 | ns |
| 1 | 2.233 | 1.286 | P > 0.05 | ns |
| 2 | 2.267 | 1.305 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 1.067 | 1.1 | 0.03333 | -5.968 to 6.034 |
| 1 | 5.633 | 7.933 | 2.3 | -3.701 to 8.301 |
| 2 | 3.233 | 4.667 | 1.433 | -4.568 to 7.434 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.03333 | 0.01919 | P > 0.05 | ns |
| 1 | 2.3 | 1.324 | P > 0.05 | ns |
| 2 | 1.433 | 0.8251 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.067 | 2.233 | 1.167 | -4.834 to 7.168 |
| 1 | 5.633 | 3.533 | -2.1 | -8.101 to 3.901 |
| 2 | 3.233 | 2.133 | -1.1 | -7.101 to 4.901 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.167 | 0.6716 | P > 0.05 | ns |
| 1 | -2.1 | 1.209 | P > 0.05 | ns |
| 2 | -1.1 | 0.6332 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.367 | 2.133 | 0.7667 | -5.234 to 6.768 |
| 1 | 5.9 | 7.867 | 1.967 | -4.034 to 7.968 |
| 2 | 3.067 | 5.5 | 2.433 | -3.568 to 8.434 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7667 | 0.4413 | P > 0.05 | ns |
| 1 | 1.967 | 1.132 | P > 0.05 | ns |
| 2 | 2.433 | 1.401 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.367 | 1.1 | -0.2667 | -6.268 to 5.734 |
| 1 | 5.9 | 7.933 | 2.033 | -3.968 to 8.034 |
| 2 | 3.067 | 4.667 | 1.6 | -4.401 to 7.601 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.2667 | 0.1535 | P > 0.05 | ns |
| 1 | 2.033 | 1.17 | P > 0.05 | ns |
| 2 | 1.6 | 0.921 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.367 | 2.233 | 0.8667 | -5.134 to 6.868 |
| 1 | 5.9 | 3.533 | -2.367 | -8.368 to 3.634 |
| 2 | 3.067 | 2.133 | -0.9333 | -6.934 to 5.068 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0.8667 | 0.4989 | P > 0.05 | ns |
| 1 | -2.367 | 1.362 | P > 0.05 | ns |
| 2 | -0.9333 | 0.5373 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.133 | 1.1 | -1.033 | -7.034 to 4.968 |
| 1 | 7.867 | 7.933 | 0.06667 | -5.934 to 6.068 |
| 2 | 5.5 | 4.667 | -0.8333 | -6.834 to 5.168 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.033 | 0.5948 | P > 0.05 | ns |
| 1 | 0.06667 | 0.03838 | P > 0.05 | ns |
| 2 | -0.8333 | 0.4797 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.133 | 2.233 | 0.1 | -5.901 to 6.101 |
| 1 | 7.867 | 3.533 | -4.333 | -10.33 to 1.668 |
| 2 | 5.5 | 2.133 | -3.367 | -9.368 to 2.634 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.1 | 0.05756 | P > 0.05 | ns |
| 1 | -4.333 | 2.494 | P > 0.05 | ns |
| 2 | -3.367 | 1.938 | P > 0.05 | ns |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.1 | 2.233 | 1.133 | -4.868 to 7.134 |
| 1 | 7.933 | 3.533 | -4.4 | -10.40 to 1.601 |
| 2 | 4.667 | 2.133 | -2.533 | -8.534 to 3.468 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.133 | 0.6524 | P > 0.05 | ns |
| 1 | -4.4 | 2.533 | P > 0.05 | ns |
| 2 | -2.533 | 1.458 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 18.4 | 0.0636 |
| Time | 34.97 | P<0.0001 |
| Treatment | 18.19 | 0.0136 |
| Subjects (matching) | 8.3496 | 0.6052 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 93.32 | 11.66 | 2.29 |
| Time | 2 | 177.4 | 88.68 | 17.41 |
| Treatment | 4 | 92.26 | 23.06 | 5.447 |
| Subjects (matching) | 10 | 42.35 | 4.235 | 0.8312 |
| Residual | 20 | 101.9 | 5.095 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.93 | 10.33 | -0.6 | -6.785 to 5.585 |
| 1 | 15.17 | 11.33 | -3.833 | -10.02 to 2.351 |
| 2 | 9.5 | 4.233 | -5.267 | -11.45 to 0.9179 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.6 | 0.3351 | P > 0.05 | ns |
| 1 | -3.833 | 2.141 | P > 0.05 | ns |
| 2 | -5.267 | 2.942 | P < 0.05 | * |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.93 | 12.77 | 1.833 | -4.351 to 8.018 |
| 1 | 15.17 | 10.7 | -4.467 | -10.65 to 1.718 |
| 2 | 9.5 | 11.5 | 2 | -4.185 to 8.185 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.833 | 1.024 | P > 0.05 | ns |
| 1 | -4.467 | 2.495 | P > 0.05 | ns |
| 2 | 2 | 1.117 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | | 10.93 | 12 | 1.067 | -5.118 to 7.251 |
| 1 | | 15.17 | 13.2 | -1.967 | -8.151 to 4.218 |
| 2 | | 9.5 | 9.667 | 0.1667 | -6.018 to 6.351 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.067 | 0.5958 | P > 0.05 | ns |
| 1 | -1.967 | 1.098 | P > 0.05 | ns |
| 2 | 0.1667 | 0.09309 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.93 | 10.1 | -0.8333 | -7.018 to 5.351 |
| 1 | 15.17 | 12.47 | -2.7 | -8.885 to 3.485 |
| 2 | 9.5 | 4.367 | -5.133 | -11.32 to 1.051 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.8333 | 0.4655 | P > 0.05 | ns |
| 1 | -2.7 | 1.508 | P > 0.05 | ns |
| 2 | -5.133 | 2.867 | P < 0.05 | * |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.33 | 12.77 | 2.433 | -3.751 to 8.618 |
| 1 | 11.33 | 10.7 | -0.6333 | -6.818 to 5.551 |
| 2 | 4.233 | 11.5 | 7.267 | 1.082 to 13.45 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.433 | 1.359 | P > 0.05 | ns |
| 1 | -0.6333 | 0.3537 | P > 0.05 | ns |
| 2 | 7.267 | 4.059 | P<0.001 | *** |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.33 | 12 | 1.667 | -4.518 to 7.851 |
| 1 | 11.33 | 13.2 | 1.867 | -4.318 to 8.051 |
| 2 | 4.233 | 9.667 | 5.433 | -0.7512 to 11.62 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.667 | 0.9309 | P > 0.05 | ns |
| 1 | 1.867 | 1.043 | P > 0.05 | ns |
| 2 | 5.433 | 3.035 | P < 0.05 | * |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.33 | 10.1 | -0.2333 | -6.418 to 5.951 |
| 1 | 11.33 | 12.47 | 1.133 | -5.051 to 7.318 |
| 2 | 4.233 | 4.367 | 0.1333 | -6.051 to 6.318 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | -0.2333 | 0.1303 | P > 0.05 | ns |
| 1 | 1.133 | 0.633 | P > 0.05 | ns |
| 2 | 0.1333 | 0.07447 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12.77 | 12 | -0.7667 | -6.951 to 5.418 |
| 1 | 10.7 | 13.2 | 2.5 | -3.685 to 8.685 |
| 2 | 11.5 | 9.667 | -1.833 | -8.018 to 4.351 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.7667 | 0.4282 | P > 0.05 | ns |
| 1 | 2.5 | 1.396 | P > 0.05 | ns |
| 2 | -1.833 | 1.024 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12.77 | 10.1 | -2.667 | -8.851 to 3.518 |
| 1 | 10.7 | 12.47 | 1.767 | -4.418 to 7.951 |
| 2 | 11.5 | 4.367 | -7.133 | -13.32 to -0.9488 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.667 | 1.489 | P > 0.05 | ns |
| 1 | 1.767 | 0.9868 | P > 0.05 | ns |
| 2 | -7.133 | 3.984 | P<0.01 | ** |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12 | 10.1 | -1.9 | -8.085 to 4.285 |
| 1 | 13.2 | 12.47 | -0.7333 | -6.918 to 5.451 |
| 2 | 9.667 | 4.367 | -5.3 | -11.48 to 0.8845 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.9 | 1.061 | P > 0.05 | ns |
| 1 | -0.7333 | 0.4096 | P > 0.05 | ns |
| 2 | -5.3 | 2.96 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 17.19 | 0.0949 |
| Time | 37.02 | P<0.0001 |
| Treatment | 9.96 | 0.2263 |
| Subjects (matching) | 14.6698 | 0.2552 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 94.82 | 11.85 | 2.032 |
| Time | 2 | 204.2 | 102.1 | 17.5 |
| Treatment | 4 | 54.96 | 13.74 | 1.698 |
| Subjects (matching) | 10 | 80.91 | 8.091 | 1.387 |
| Residual | 20 | 116.6 | 5.832 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.567 | 7.2 | -1.367 | -8.604 to 5.871 |
| 1 | 14.5 | 11.37 | -3.133 | -10.37 to 4.104 |
| 2 | 10.53 | 6.4 | -4.133 | -11.37 to 3.104 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.367 | 0.6523 | P > 0.05 | ns |
| 1 | -3.133 | 1.495 | P > 0.05 | ns |
| 2 | -4.133 | 1.973 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.567 | 8.367 | -0.2 | -7.438 to 7.038 |
| 1 | 14.5 | 11.33 | -3.167 | -10.40 to 4.071 |
| 2 | 10.53 | 13.6 | 3.067 | -4.171 to 10.30 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.2 | 0.09545 | P > 0.05 | ns |
| 1 | -3.167 | 1.511 | P > 0.05 | ns |
| 2 | 3.067 | 1.464 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | 8.567 | 7.633 | -0.9333 | -8.171 to 6.304 | |
| 1 | 14.5 | 13.13 | -1.367 | -8.604 to 5.871 | |
| 2 | 10.53 | 12.57 | 2.033 | -5.204 to 9.271 | |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9333 | 0.4455 | P > 0.05 | ns |
| 1 | -1.367 | 0.6523 | P > 0.05 | ns |
| 2 | 2.033 | 0.9704 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.567 | 6.133 | -2.433 | -9.671 to 4.804 |
| 1 | 14.5 | 12.43 | -2.067 | -9.304 to 5.171 |
| 2 | 10.53 | 14.07 | 3.533 | -3.704 to 10.77 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.433 | 1.161 | P > 0.05 | ns |
| 1 | -2.067 | 0.9864 | P > 0.05 | ns |
| 2 | 3.533 | 1.686 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.2 | 8.367 | 1.167 | -6.071 to 8.404 |
| 1 | 11.37 | 11.33 | -0.03333 | -7.271 to 7.204 |
| 2 | 6.4 | 13.6 | 7.2 | -0.03778 to 14.44 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.167 | 0.5568 | P > 0.05 | ns |
| 1 | -0.03333 | 0.01591 | P > 0.05 | ns |
| 2 | 7.2 | 3.436 | P<0.01 | ** |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.2 | 7.633 | 0.4333 | -6.804 to 7.671 |
| 1 | 11.37 | 13.13 | 1.767 | -5.471 to 9.004 |
| 2 | 6.4 | 12.57 | 6.167 | -1.071 to 13.40 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.4333 | 0.2068 | P > 0.05 | ns |
| 1 | 1.767 | 0.8432 | P > 0.05 | ns |
| 2 | 6.167 | 2.943 | P < 0.05 | * |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.2 | 6.133 | -1.067 | -8.304 to 6.171 |
| 1 | 11.37 | 12.43 | 1.067 | -6.171 to 8.304 |
| 2 | 6.4 | 14.07 | 7.667 | 0.4289 to 14.90 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.067 | 0.5091 | P > 0.05 | ns |
| 1 | 1.067 | 0.5091 | P > 0.05 | ns |
| 2 | 7.667 | 3.659 | P<0.01 | ** |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.367 | 7.633 | -0.7333 | -7.971 to 6.504 |
| 1 | 11.33 | 13.13 | 1.8 | -5.438 to 9.038 |
| 2 | 13.6 | 12.57 | -1.033 | -8.271 to 6.204 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.7333 | 0.35 | P > 0.05 | ns |
| 1 | 1.8 | 0.8591 | P > 0.05 | ns |
| 2 | -1.033 | 0.4932 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.367 | 6.133 | -2.233 | -9.471 to 5.004 |
| 1 | 11.33 | 12.43 | 1.1 | -6.138 to 8.338 |
| 2 | 13.6 | 14.07 | 0.4667 | -6.771 to 7.704 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.233 | 1.066 | P > 0.05 | ns |
| 1 | 1.1 | 0.525 | P > 0.05 | ns |
| 2 | 0.4667 | 0.2227 | P > 0.05 | ns |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.633 | 6.133 | -1.5 | -8.738 to 5.738 |
| 1 | 13.13 | 12.43 | -0.7 | -7.938 to 6.538 |
| 2 | 12.57 | 14.07 | 1.5 | -5.738 to 8.738 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.5 | 0.7159 | P > 0.05 | ns |
| 1 | -0.7 | 0.3341 | P > 0.05 | ns |
| 2 | 1.5 | 0.7159 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 20.56 | 0.1225 |
| Time | 14.89 | 0.0132 |
| Treatment | 27.09 | 0.0066 |
| Subjects (matching) | 9.9811 | 0.692 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | * | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 67.56 | 8.445 | 1.869 |
| Time | 2 | 48.93 | 24.46 | 5.415 |
| Treatment | 4 | 89.02 | 22.25 | 6.784 |
| Subjects (matching) | 10 | 32.8 | 3.28 | 0.7262 |
| Residual | 20 | 90.34 | 4.517 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.767 | 6.333 | -1.433 | -7.148 to 4.281 |
| 1 | 12.53 | 7.567 | -4.967 | -10.68 to 0.7478 |
| 2 | 8.367 | 3.067 | -5.3 | -11.01 to 0.4145 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.433 | 0.8664 | P > 0.05 | ns |
| 1 | -4.967 | 3.002 | P < 0.05 | * |
| 2 | -5.3 | 3.204 | P<0.01 | ** |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.767 | 7.4 | -0.3667 | -6.081 to 5.348 |
| 1 | 12.53 | 9.767 | -2.767 | -8.481 to 2.948 |
| 2 | 8.367 | 8.467 | 0.1 | -5.614 to 5.814 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.3667 | 0.2216 | P > 0.05 | ns |
| 1 | -2.767 | 1.672 | P > 0.05 | ns |
| 2 | 0.1 | 0.06045 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 7.767 | 7.733 | -0.03333 | -5.748 to 5.681 |
| 1 | 12.53 | 8.7 | -3.833 | -9.548 to 1.881 |
| 2 | 8.367 | 10.43 | 2.067 | -3.648 to 7.781 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.03333 | 0.02015 | P > 0.05 | ns |
| 1 | -3.833 | 2.317 | P > 0.05 | ns |
| 2 | 2.067 | 1.249 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.767 | 6.933 | -0.8333 | -6.548 to 4.881 |
| 1 | 12.53 | 10.23 | -2.3 | -8.014 to 3.414 |
| 2 | 8.367 | 10.53 | 2.167 | -3.548 to 7.881 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.8333 | 0.5037 | P > 0.05 | ns |
| 1 | -2.3 | 1.39 | P > 0.05 | ns |
| 2 | 2.167 | 1.31 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.333 | 7.4 | 1.067 | -4.648 to 6.781 |
| 1 | 7.567 | 9.767 | 2.2 | -3.514 to 7.914 |
| 2 | 3.067 | 8.467 | 5.4 | -0.3145 to 11.11 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.067 | 0.6448 | P > 0.05 | ns |
| 1 | 2.2 | 1.33 | P > 0.05 | ns |
| 2 | 5.4 | 3.264 | P<0.01 | ** |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.333 | 7.733 | 1.4 | -4.314 to 7.114 |
| 1 | 7.567 | 8.7 | 1.133 | -4.581 to 6.848 |
| 2 | 3.067 | 10.43 | 7.367 | 1.652 to 13.08 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.4 | 0.8463 | P > 0.05 | ns |
| 1 | 1.133 | 0.6851 | P > 0.05 | ns |
| 2 | 7.367 | 4.453 | P<0.001 | *** |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 6.333 | 6.933 | 0.6 | -5.114 to 6.314 |
| 1 | 7.567 | 10.23 | 2.667 | -3.048 to 8.381 |
| 2 | 3.067 | 10.53 | 7.467 | 1.752 to 13.18 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0.6 | 0.3627 | P > 0.05 | ns |
| 1 | 2.667 | 1.612 | P > 0.05 | ns |
| 2 | 7.467 | 4.514 | P<0.001 | *** |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.4 | 7.733 | 0.3333 | -5.381 to 6.048 |
| 1 | 9.767 | 8.7 | -1.067 | -6.781 to 4.648 |
| 2 | 8.467 | 10.43 | 1.967 | -3.748 to 7.681 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.3333 | 0.2015 | P > 0.05 | ns |
| 1 | -1.067 | 0.6448 | P > 0.05 | ns |
| 2 | 1.967 | 1.189 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.4 | 6.933 | -0.4667 | -6.181 to 5.248 |
| 1 | 9.767 | 10.23 | 0.4667 | -5.248 to 6.181 |
| 2 | 8.467 | 10.53 | 2.067 | -3.648 to 7.781 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4667 | 0.2821 | P > 0.05 | ns |
| 1 | 0.4667 | 0.2821 | P > 0.05 | ns |
| 2 | 2.067 | 1.249 | P > 0.05 | ns |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.733 | 6.933 | -0.8 | -6.514 to 4.914 |
| 1 | 8.7 | 10.23 | 1.533 | -4.181 to 7.248 |
| 2 | 10.43 | 10.53 | 0.1 | -5.614 to 5.814 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.8 | 0.4836 | P > 0.05 | ns |
| 1 | 1.533 | 0.9269 | P > 0.05 | ns |
| 2 | 0.1 | 0.06045 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 13.68 | 0.237 |
| Time | 34.97 | 0.0001 |
| Treatment | 20.56 | 0.0055 |
| Subjects (matching) | 7.1933 | 0.7878 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 53.27 | 6.658 | 1.45 |
| Time | 2 | 136.2 | 68.09 | 14.82 |
| Treatment | 4 | 80.06 | 20.02 | 7.146 |
| Subjects (matching) | 10 | 28.01 | 2.801 | 0.6098 |
| Residual | 20 | 91.86 | 4.593 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5333 | 0.4333 | -0.1 | -5.738 to 5.538 |
| 1 | 5.133 | 3.467 | -1.667 | -7.305 to 3.971 |
| 2 | 5.3 | 3.067 | -2.233 | -7.871 to 3.405 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1 | 0.06127 | P > 0.05 | ns |
| 1 | -1.667 | 1.021 | P > 0.05 | ns |
| 2 | -2.233 | 1.368 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5333 | 2.433 | 1.9 | -3.738 to 7.538 |
| 1 | 5.133 | 7.867 | 2.733 | -2.905 to 8.371 |
| 2 | 5.3 | 6.667 | 1.367 | -4.271 to 7.005 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.9 | 1.164 | P > 0.05 | ns |
| 1 | 2.733 | 1.675 | P > 0.05 | ns |
| 2 | 1.367 | 0.8374 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | | 0.5333 | 1.133 | 0.6 | -5.038 to 6.238 |
| 1 | | 5.133 | 7.933 | 2.8 | -2.838 to 8.438 |
| 2 | | 5.3 | 6.333 | 1.033 | -4.605 to 6.671 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6 | 0.3676 | P > 0.05 | ns |
| 1 | 2.8 | 1.716 | P > 0.05 | ns |
| 2 | 1.033 | 0.6331 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5333 | 2.533 | 2 | -3.638 to 7.638 |
| 1 | 5.133 | 1.733 | -3.4 | -9.038 to 2.238 |
| 2 | 5.3 | 3.467 | -1.833 | -7.471 to 3.805 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2 | 1.225 | P > 0.05 | ns |
| 1 | -3.4 | 2.083 | P > 0.05 | ns |
| 2 | -1.833 | 1.123 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.4333 | 2.433 | 2 | -3.638 to 7.638 |
| 1 | 3.467 | 7.867 | 4.4 | -1.238 to 10.04 |
| 2 | 3.067 | 6.667 | 3.6 | -2.038 to 9.238 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2 | 1.225 | P > 0.05 | ns |
| 1 | 4.4 | 2.696 | P < 0.05 | * |
| 2 | 3.6 | 2.206 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.4333 | 1.133 | 0.7 | -4.938 to 6.338 |
| 1 | 3.467 | 7.933 | 4.467 | -1.171 to 10.10 |
| 2 | 3.067 | 6.333 | 3.267 | -2.371 to 8.905 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7 | 0.4289 | P > 0.05 | ns |
| 1 | 4.467 | 2.737 | P < 0.05 | * |
| 2 | 3.267 | 2.001 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.4333 | 2.533 | 2.1 | -3.538 to 7.738 |
| 1 | 3.467 | 1.733 | -1.733 | -7.371 to 3.905 |
| 2 | 3.067 | 3.467 | 0.4 | -5.238 to 6.038 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 2.1 | 1.287 | P > 0.05 | ns |
| 1 | -1.733 | 1.062 | P > 0.05 | ns |
| 2 | 0.4 | 0.2451 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.433 | 1.133 | -1.3 | -6.938 to 4.338 |
| 1 | 7.867 | 7.933 | 0.06667 | -5.571 to 5.705 |
| 2 | 6.667 | 6.333 | -0.3333 | -5.971 to 5.305 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.3 | 0.7965 | P > 0.05 | ns |
| 1 | 0.06667 | 0.04085 | P > 0.05 | ns |
| 2 | -0.3333 | 0.2042 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.433 | 2.533 | 0.1 | -5.538 to 5.738 |
| 1 | 7.867 | 1.733 | -6.133 | -11.77 to -0.4953 |
| 2 | 6.667 | 3.467 | -3.2 | -8.838 to 2.438 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.1 | 0.06127 | P > 0.05 | ns |
| 1 | -6.133 | 3.758 | P<0.01 | ** |
| 2 | -3.2 | 1.961 | P > 0.05 | ns |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.133 | 2.533 | 1.4 | -4.238 to 7.038 |
| 1 | 7.933 | 1.733 | -6.2 | -11.84 to -0.5620 |
| 2 | 6.333 | 3.467 | -2.867 | -8.505 to 2.771 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.4 | 0.8578 | P > 0.05 | ns |
| 1 | -6.2 | 3.799 | P<0.01 | ** |
| 2 | -2.867 | 1.756 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 8.5 | 0.4338 |
| Time | 43.68 | P<0.0001 |
| Treatment | 23.27 | 0.0005 |
| Subjects (matching) | 4.3076 | 0.9171 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 45.2 | 5.65 | 1.05 |
| Time | 2 | 232.2 | 116.1 | 21.58 |
| Treatment | 4 | 123.7 | 30.93 | 13.51 |
| Subjects (matching) | 10 | 22.9 | 2.29 | 0.4256 |
| Residual | 20 | 107.6 | 5.381 | |

Bonferroni posttests

Neo A 10-8 vs. Neo A 10-9

| Treatment | Neo A 10-8 | Neo A 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.367 | 2.2 | -0.1667 | -6.050 to 5.716 |
| 1 | 0.1667 | 2.767 | 2.6 | -3.283 to 8.483 |
| 2 | 4.233 | 5.633 | 1.4 | -4.483 to 7.283 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1667 | 0.09786 | P > 0.05 | ns |
| 1 | 2.6 | 1.527 | P > 0.05 | ns |
| 2 | 1.4 | 0.8221 | P > 0.05 | ns |

Neo A 10-8 vs. Neo A 10-10

| Treatment | Neo A 10-8 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.367 | 3.867 | 1.5 | -4.383 to 7.383 |
| 1 | 0.1667 | 3.933 | 3.767 | -2.116 to 9.650 |
| 2 | 4.233 | 9.733 | 5.5 | -0.3829 to 11.38 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.5 | 0.8808 | P > 0.05 | ns |
| 1 | 3.767 | 2.212 | P > 0.05 | ns |
| 2 | 5.5 | 3.23 | P<0.01 | ** |

Neo A 10-8 vs. Neo A 10-11

| Treatment | Neo A 10-8 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | 2.367 | 2.9 | 0.5333 | -5.350 to 6.416 |
| 1 | 0.1667 | 5.1 | 4.933 | -0.9496 to 10.82 |
| 2 | 4.233 | 11.53 | 7.3 | 1.417 to 13.18 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.5333 | 0.3132 | P > 0.05 | ns |
| 1 | 4.933 | 2.897 | P < 0.05 | * |
| 2 | 7.3 | 4.286 | P<0.001 | *** |

Neo A 10-8 vs. Neo A 10-12

| Treatment | Neo A 10-8 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.367 | 4.033 | 1.667 | -4.216 to 7.550 |
| 1 | 0.1667 | 5.1 | 4.933 | -0.9496 to 10.82 |
| 2 | 4.233 | 9.133 | 4.9 | -0.9829 to 10.78 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.667 | 0.9787 | P > 0.05 | ns |
| 1 | 4.933 | 2.897 | P < 0.05 | * |
| 2 | 4.9 | 2.877 | P < 0.05 | * |

Neo A 10-9 vs. Neo A 10-10

| Treatment | Neo A 10-9 | Neo A 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.2 | 3.867 | 1.667 | -4.216 to 7.550 |
| 1 | 2.767 | 3.933 | 1.167 | -4.716 to 7.050 |
| 2 | 5.633 | 9.733 | 4.1 | -1.783 to 9.983 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.667 | 0.9787 | P > 0.05 | ns |
| 1 | 1.167 | 0.6851 | P > 0.05 | ns |
| 2 | 4.1 | 2.407 | P > 0.05 | ns |

Neo A 10-9 vs. Neo A 10-11

| Treatment | Neo A 10-9 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.2 | 2.9 | 0.7 | -5.183 to 6.583 |
| 1 | 2.767 | 5.1 | 2.333 | -3.550 to 8.216 |
| 2 | 5.633 | 11.53 | 5.9 | 0.01711 to 11.78 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7 | 0.411 | P > 0.05 | ns |
| 1 | 2.333 | 1.37 | P > 0.05 | ns |
| 2 | 5.9 | 3.464 | P<0.01 | ** |

Neo A 10-9 vs. Neo A 10-12

| Treatment | Neo A 10-9 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.2 | 4.033 | 1.833 | -4.050 to 7.716 |
| 1 | 2.767 | 5.1 | 2.333 | -3.550 to 8.216 |
| 2 | 5.633 | 9.133 | 3.5 | -2.383 to 9.383 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.833 | 1.077 | P > 0.05 | ns |
| 1 | 2.333 | 1.37 | P > 0.05 | ns |
| 2 | 3.5 | 2.055 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-11

| Treatment | Neo A 10-10 | Neo A 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.867 | 2.9 | -0.9667 | -6.850 to 4.916 |
| 1 | 3.933 | 5.1 | 1.167 | -4.716 to 7.050 |
| 2 | 9.733 | 11.53 | 1.8 | -4.083 to 7.683 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9667 | 0.5676 | P > 0.05 | ns |
| 1 | 1.167 | 0.6851 | P > 0.05 | ns |
| 2 | 1.8 | 1.057 | P > 0.05 | ns |

Neo A 10-10 vs. Neo A 10-12

| Treatment | Neo A 10-10 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.867 | 4.033 | 0.1667 | -5.716 to 6.050 |
| 1 | 3.933 | 5.1 | 1.167 | -4.716 to 7.050 |
| 2 | 9.733 | 9.133 | -0.6 | -6.483 to 5.283 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.1667 | 0.09786 | P > 0.05 | ns |
| 1 | 1.167 | 0.6851 | P > 0.05 | ns |
| 2 | -0.6 | 0.3523 | P > 0.05 | ns |

Neo A 10-11 vs. Neo A 10-12

| Treatment | Neo A 10-11 | Neo A 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.9 | 4.033 | 1.133 | -4.750 to 7.016 |
| 1 | 5.1 | 5.1 | 4.768E-07 | -5.883 to 5.883 |
| 2 | 11.53 | 9.133 | -2.4 | -8.283 to 3.483 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.133 | 0.6655 | P > 0.05 | ns |
| 1 | 4.768E-07 | 0.00000028 | P > 0.05 | ns |
| 2 | -2.4 | 1.409 | P > 0.05 | ns |

## APPENDIX VI – ANOVA TABLES Neo B Dose Dependence

| | |
|---|---|
| Table Analyzed | Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 28.19 | 0.0211 |
| Time | 3.56 | 0.2407 |
| Treatment | 21.07 | 0.1419 |
| Subjects (matching) | 23.9183 | 0.0815 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 156.1 | 19.51 | 3.03 |
| Time | 2 | 19.71 | 9.854 | 1.531 |
| Treatment | 4 | 116.7 | 29.16 | 2.203 |
| Subjects (matching) | 10 | 132.4 | 13.24 | 2.057 |
| Residual | 20 | 128.8 | 6.438 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.5 | 0.9 | -3.6 | -11.92 to 4.722 |
| 1 | 10.3 | 1.267 | -9.033 | -17.36 to -0.7115 |
| 2 | 2.933 | 6 | 3.067 | -5.255 to 11.39 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.6 | 1.494 | P > 0.05 | ns |
| 1 | -9.033 | 3.75 | P<0.01 | ** |
| 2 | 3.067 | 1.273 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.5 | 4.567 | 0.06667 | -8.255 to 8.388 |
| 1 | 10.3 | 1.633 | -8.667 | -16.99 to -0.3449 |
| 2 | 2.933 | 5.633 | 2.7 | -5.622 to 11.02 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.06667 | 0.02767 | P > 0.05 | ns |
| 1 | -8.667 | 3.598 | P<0.01 | ** |
| 2 | 2.7 | 1.121 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.5 | 2.2 | -2.3 | -10.62 to 6.022 |
| 1 | 10.3 | 2.233 | -8.067 | -16.39 to 0.2551 |
| 2 | 2.933 | 3.533 | 0.6 | -7.722 to 8.922 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.3 | 0.9547 | P > 0.05 | ns |
| 1 | -8.067 | 3.348 | P<0.01 | ** |
| 2 | 0.6 | 0.2491 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.5 | 0.1667 | -4.333 | -12.66 to 3.988 |
| 1 | 10.3 | 0.7 | -9.6 | -17.92 to -1.278 |
| 2 | 2.933 | 2.333 | -0.6 | -8.922 to 7.722 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.333 | 1.799 | P > 0.05 | ns |
| 1 | -9.6 | 3.985 | P<0.01 | ** |
| 2 | -0.6 | 0.2491 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.9 | 4.567 | 3.667 | -4.655 to 11.99 |
| 1 | 1.267 | 1.633 | 0.3667 | -7.955 to 8.688 |
| 2 | 6 | 5.633 | -0.3667 | -8.688 to 7.955 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.667 | 1.522 | P > 0.05 | ns |
| 1 | 0.3667 | 0.1522 | P > 0.05 | ns |
| 2 | -0.3667 | 0.1522 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.9 | 2.2 | 1.3 | -7.022 to 9.622 |
| 1 | 1.267 | 2.233 | 0.9667 | -7.355 to 9.288 |
| 2 | 6 | 3.533 | -2.467 | -10.79 to 5.855 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.3 | 0.5396 | P > 0.05 | ns |
| 1 | 0.9667 | 0.4013 | P > 0.05 | ns |
| 2 | -2.467 | 1.024 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.9 | 0.1667 | -0.7333 | -9.055 to 7.588 |
| 1 | 1.267 | 0.7 | -0.5667 | -8.888 to 7.755 |

| | | | | |
|---|---|---|---|---|
| 2 | 6 | 2.333 | -3.667 | -11.99 to 4.655 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.7333 | 0.3044 | P > 0.05 | ns |
| 1 | -0.5667 | 0.2352 | P > 0.05 | ns |
| 2 | -3.667 | 1.522 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.567 | 2.2 | -2.367 | -10.69 to 5.955 |
| 1 | 1.633 | 2.233 | 0.6 | -7.722 to 8.922 |
| 2 | 5.633 | 3.533 | -2.1 | -10.42 to 6.222 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.367 | 0.9824 | P > 0.05 | ns |
| 1 | 0.6 | 0.2491 | P > 0.05 | ns |
| 2 | -2.1 | 0.8717 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.567 | 0.1667 | -4.4 | -12.72 to 3.922 |
| 1 | 1.633 | 0.7 | -0.9333 | -9.255 to 7.388 |
| 2 | 5.633 | 2.333 | -3.3 | -11.62 to 5.022 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.4 | 1.826 | P > 0.05 | ns |
| 1 | -0.9333 | 0.3874 | P > 0.05 | ns |
| 2 | -3.3 | 1.37 | P > 0.05 | ns |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.2 | 0.1667 | -2.033 | -10.36 to 6.288 |
| 1 | 2.233 | 0.7 | -1.533 | -9.855 to 6.788 |
| 2 | 3.533 | 2.333 | -1.2 | -9.522 to 7.122 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.033 | 0.844 | P > 0.05 | ns |
| 1 | -1.533 | 0.6365 | P > 0.05 | ns |
| 2 | -1.2 | 0.4981 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 48.77 | 0.0036 |
| Time | 5.75 | 0.1545 |
| Treatment | 9.11 | 0.0903 |
| Subjects (matching) | 8.3535 | 0.7984 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 239.4 | 29.92 | 4.353 |
| Time | 2 | 28.22 | 14.11 | 2.053 |
| Treatment | 4 | 44.72 | 11.18 | 2.727 |
| Subjects (matching) | 10 | 41 | 4.1 | 0.5965 |
| Residual | 20 | 137.5 | 6.873 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.967 | 1.767 | -0.2 | -7.079 to 6.679 |
| 1 | 7.567 | 1.267 | -6.3 | -13.18 to 0.5790 |
| 2 | 4.167 | 6 | 1.833 | -5.046 to 8.712 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.2 | 0.1004 | P > 0.05 | ns |
| 1 | -6.3 | 3.164 | P < 0.05 | * |
| 2 | 1.833 | 0.9206 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.967 | 10.23 | 8.267 | 1.388 to 15.15 |
| 1 | 7.567 | 1.633 | -5.933 | -12.81 to 0.9457 |
| 2 | 4.167 | 5.067 | 0.9 | -5.979 to 7.779 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 8.267 | 4.151 | P<0.001 | *** |
| 1 | -5.933 | 2.979 | P < 0.05 | * |
| 2 | 0.9 | 0.4519 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| | | | | | 0.05433 to |
| | 0.5 | 1.967 | 8.9 | 6.933 | 13.81 |
| | 1 | 7.567 | 3.333 | -4.233 | -11.11 to 2.646 |
| | 2 | 4.167 | 3.533 | -0.6333 | -7.512 to 6.246 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 6.933 | 3.482 | P<0.01 | ** |
| 1 | -4.233 | 2.126 | P > 0.05 | ns |
| 2 | -0.6333 | 0.318 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.967 | 4.4 | 2.433 | -4.446 to 9.312 |
| 1 | 7.567 | 3.9 | -3.667 | -10.55 to 3.212 |
| 2 | 4.167 | 2.333 | -1.833 | -8.712 to 5.046 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.433 | 1.222 | P > 0.05 | ns |
| 1 | -3.667 | 1.841 | P > 0.05 | ns |
| 2 | -1.833 | 0.9206 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.767 | 10.23 | 8.467 | 1.588 to 15.35 |
| 1 | 1.267 | 1.633 | 0.3667 | -6.512 to 7.246 |
| 2 | 6 | 5.067 | -0.9333 | -7.812 to 5.946 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 8.467 | 4.252 | P<0.001 | *** |
| 1 | 0.3667 | 0.1841 | P > 0.05 | ns |
| 2 | -0.9333 | 0.4687 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.767 | 8.9 | 7.133 | 0.2543 to 14.01 |
| 1 | 1.267 | 3.333 | 2.067 | -4.812 to 8.946 |
| 2 | 6 | 3.533 | -2.467 | -9.346 to 4.412 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 7.133 | 3.582 | P<0.01 | ** |
| 1 | 2.067 | 1.038 | P > 0.05 | ns |
| 2 | -2.467 | 1.239 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.767 | 4.4 | 2.633 | -4.246 to 9.512 |
| 1 | 1.267 | 3.9 | 2.633 | -4.246 to 9.512 |
| 2 | 6 | 2.333 | -3.667 | -10.55 to 3.212 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.633 | 1.322 | P > 0.05 | ns |
| 1 | 2.633 | 1.322 | P > 0.05 | ns |
| 2 | -3.667 | 1.841 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.23 | 8.9 | -1.333 | -8.212 to 5.546 |
| 1 | 1.633 | 3.333 | 1.7 | -5.179 to 8.579 |
| 2 | 5.067 | 3.533 | -1.533 | -8.412 to 5.346 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.333 | 0.6695 | P > 0.05 | ns |
| 1 | 1.7 | 0.8537 | P > 0.05 | ns |
| 2 | -1.533 | 0.77 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 10.23 | 4.4 | -5.833 | -12.71 to 1.046 |
| 1 | 1.633 | 3.9 | 2.267 | -4.612 to 9.146 |
| 2 | 5.067 | 2.333 | -2.733 | -9.612 to 4.146 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -5.833 | 2.929 | P < 0.05 | * |
| 1 | 2.267 | 1.138 | P > 0.05 | ns |
| 2 | -2.733 | 1.373 | P > 0.05 | ns |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.9 | 4.4 | -4.5 | -11.38 to 2.379 |
| 1 | 3.333 | 3.9 | 0.5667 | -6.312 to 7.446 |
| 2 | 3.533 | 2.333 | -1.2 | -8.079 to 5.679 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.5 | 2.26 | P > 0.05 | ns |
| 1 | 0.5667 | 0.2846 | P > 0.05 | ns |
| 2 | -1.2 | 0.6026 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 62.3 | P<0.0001 |
| Time | 10.63 | 0.0013 |
| Treatment | 3.82 | 0.5524 |
| Subjects (matching) | 11.9502 | 0.0739 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | ** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 455 | 56.87 | 13.78 |
| Time | 2 | 77.61 | 38.8 | 9.402 |
| Treatment | 4 | 27.9 | 6.975 | 0.7993 |
| Subjects (matching) | 10 | 87.27 | 8.727 | 2.115 |
| *Residual* | 20 | 82.54 | 4.127 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.833 | 9.067 | -0.7667 | -7.477 to 5.944 |
| 1 | 14.17 | 10.97 | -3.2 | -9.910 to 3.510 |
| 2 | 10.43 | 10.57 | 0.1333 | -6.577 to 6.844 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.7667 | 0.3947 | P > 0.05 | ns |
| 1 | -3.2 | 1.647 | P > 0.05 | ns |
| 2 | 0.1333 | 0.06864 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.833 | 15.17 | 5.333 | -1.377 to 12.04 |
| 1 | 14.17 | 1.533 | -12.63 | -19.34 to -5.923 |
| 2 | 10.43 | 11.7 | 1.267 | -5.444 to 7.977 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.333 | 2.745 | P < 0.05 | * |
| 1 | -12.63 | 6.503 | P<0.001 | *** |
| 2 | 1.267 | 0.6521 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 9.833 | 14.5 | 4.667 | -2.044 to 11.38 |
| 1 | 14.17 | 10.7 | -3.467 | -10.18 to 3.244 |
| 2 | 10.43 | 6.6 | -3.833 | -10.54 to 2.877 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.667 | 2.402 | P > 0.05 | ns |
| 1 | -3.467 | 1.785 | P > 0.05 | ns |
| 2 | -3.833 | 1.973 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.833 | 11.23 | 1.4 | -5.310 to 8.110 |
| 1 | 14.17 | 12.07 | -2.1 | -8.810 to 4.610 |
| 2 | 10.43 | 4.667 | -5.767 | -12.48 to 0.9437 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.4 | 0.7207 | P > 0.05 | ns |
| 1 | -2.1 | 1.081 | P > 0.05 | ns |
| 2 | -5.767 | 2.969 | P < 0.05 | * |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.067 | 15.17 | 6.1 | -0.6104 to 12.81 |
| 1 | 10.97 | 1.533 | -9.433 | -16.14 to -2.723 |
| 2 | 10.57 | 11.7 | 1.133 | -5.577 to 7.844 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 6.1 | 3.14 | P < 0.05 | * |
| 1 | -9.433 | 4.856 | P<0.001 | *** |
| 2 | 1.133 | 0.5834 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.067 | 14.5 | 5.433 | -1.277 to 12.14 |
| 1 | 10.97 | 10.7 | -0.2667 | -6.977 to 6.444 |
| 2 | 10.57 | 6.6 | -3.967 | -10.68 to 2.744 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.433 | 2.797 | P < 0.05 | * |
| 1 | -0.2667 | 0.1373 | P > 0.05 | ns |
| 2 | -3.967 | 2.042 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 9.067 | 11.23 | 2.167 | -4.544 to 8.877 |
| 1 | 10.97 | 12.07 | 1.1 | -5.610 to 7.810 |
| 2 | 10.57 | 4.667 | -5.9 | -12.61 to 0.8104 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 2.167 | 1.115 | P > 0.05 | ns |
| 1 | 1.1 | 0.5663 | P > 0.05 | ns |
| 2 | -5.9 | 3.037 | P < 0.05 | * |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.17 | 14.5 | -0.6667 | -7.377 to 6.044 |
| 1 | 1.533 | 10.7 | 9.167 | 2.456 to 15.88 |
| 2 | 11.7 | 6.6 | -5.1 | -11.81 to 1.610 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.6667 | 0.3432 | P > 0.05 | ns |
| 1 | 9.167 | 4.719 | P<0.001 | *** |
| 2 | -5.1 | 2.625 | P < 0.05 | * |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 15.17 | 11.23 | -3.933 | -10.64 to 2.777 |
| 1 | 1.533 | 12.07 | 10.53 | 3.823 to 17.24 |
| 2 | 11.7 | 4.667 | -7.033 | -13.74 to -0.3229 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.933 | 2.025 | P > 0.05 | ns |
| 1 | 10.53 | 5.422 | P<0.001 | *** |
| 2 | -7.033 | 3.621 | P<0.01 | ** |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 14.5 | 11.23 | -3.267 | -9.977 to 3.444 |
| 1 | 10.7 | 12.07 | 1.367 | -5.344 to 8.077 |
| 2 | 6.6 | 4.667 | -1.933 | -8.644 to 4.777 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -3.267 | 1.682 | P > 0.05 | ns |
| 1 | 1.367 | 0.7035 | P > 0.05 | ns |
| 2 | -1.933 | 0.9952 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 50.21 | 0.0014 |
| Time | 2.65 | 0.3582 |
| Treatment | 8.77 | 0.2547 |
| Subjects (matching) | 13.9066 | 0.3849 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 380.3 | 47.53 | 5.129 |
| Time | 2 | 20.04 | 10.02 | 1.081 |
| Treatment | 4 | 66.39 | 16.6 | 1.576 |
| Subjects (matching) | 10 | 105.3 | 10.53 | 1.137 |
| Residual | 20 | 185.3 | 9.267 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.567 | 7.467 | -1.1 | -9.879 to 7.679 |
| 1 | 14.5 | 10.83 | -3.667 | -12.45 to 5.113 |
| 2 | 11.77 | 10.93 | -0.8333 | -9.613 to 7.946 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -1.1 | 0.4328 | P > 0.05 | ns |
| 1 | -3.667 | 1.443 | P > 0.05 | ns |
| 2 | -0.8333 | 0.3279 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.567 | 13.73 | 5.167 | -3.613 to 13.95 |
| 1 | 14.5 | 2.6 | -11.9 | -20.68 to -3.121 |
| 2 | 11.77 | 9.233 | -2.533 | -11.31 to 6.246 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.167 | 2.033 | P > 0.05 | ns |
| 1 | -11.9 | 4.682 | P<0.001 | *** |
| 2 | -2.533 | 0.9968 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | | 8.567 | 13.17 | 4.6 | -4.179 to 13.38 |
| 1 | | 14.5 | 11.2 | -3.3 | -12.08 to 5.479 |
| 2 | | 11.77 | 5.5 | -6.267 | -15.05 to 2.513 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.6 | 1.81 | P > 0.05 | ns |
| 1 | -3.3 | 1.298 | P > 0.05 | ns |
| 2 | -6.267 | 2.466 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 8.567 | 7.667 | -0.9 | -9.679 to 7.879 |
| 1 | 14.5 | 11 | -3.5 | -12.28 to 5.279 |
| 2 | 11.77 | 5.867 | -5.9 | -14.68 to 2.879 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9 | 0.3541 | P > 0.05 | ns |
| 1 | -3.5 | 1.377 | P > 0.05 | ns |
| 2 | -5.9 | 2.321 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 13.73 | 6.267 | -2.513 to 15.05 |
| 1 | 10.83 | 2.6 | -8.233 | -17.01 to 0.5460 |
| 2 | 10.93 | 9.233 | -1.7 | -10.48 to 7.079 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 6.267 | 2.466 | P > 0.05 | ns |
| 1 | -8.233 | 3.24 | P<0.01 | ** |
| 2 | -1.7 | 0.6689 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 13.17 | 5.7 | -3.079 to 14.48 |
| 1 | 10.83 | 11.2 | 0.3667 | -8.413 to 9.146 |
| 2 | 10.93 | 5.5 | -5.433 | -14.21 to 3.346 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.7 | 2.243 | P > 0.05 | ns |
| 1 | 0.3667 | 0.1443 | P > 0.05 | ns |
| 2 | -5.433 | 2.138 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.467 | 7.667 | 0.2 | -8.579 to 8.979 |
| 1 | 10.83 | 11 | 0.1667 | -8.613 to 8.946 |
| 2 | 10.93 | 5.867 | -5.067 | -13.85 to 3.713 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0.2 | 0.07869 | P > 0.05 | ns |
| 1 | 0.1667 | 0.06558 | P > 0.05 | ns |
| 2 | -5.067 | 1.994 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 13.73 | 13.17 | -0.5667 | -9.346 to 8.213 |
| 1 | 2.6 | 11.2 | 8.6 | -0.1793 to 17.38 |
| 2 | 9.233 | 5.5 | -3.733 | -12.51 to 5.046 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5667 | 0.223 | P > 0.05 | ns |
| 1 | 8.6 | 3.384 | P<0.01 | ** |
| 2 | -3.733 | 1.469 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 13.73 | 7.667 | -6.067 | -14.85 to 2.713 |
| 1 | 2.6 | 11 | 8.4 | -0.3793 to 17.18 |
| 2 | 9.233 | 5.867 | -3.367 | -12.15 to 5.413 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6.067 | 2.387 | P > 0.05 | ns |
| 1 | 8.4 | 3.305 | P<0.01 | ** |
| 2 | -3.367 | 1.325 | P > 0.05 | ns |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 13.17 | 7.667 | -5.5 | -14.28 to 3.279 |
| 1 | 11.2 | 11 | -0.2 | -8.979 to 8.579 |
| 2 | 5.5 | 5.867 | 0.3667 | -8.413 to 9.146 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -5.5 | 2.164 | P > 0.05 | ns |
| 1 | -0.2 | 0.07869 | P > 0.05 | ns |
| 2 | 0.3667 | 0.1443 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 62.42 | P<0.0001 |
| Time | 1.21 | 0.5421 |
| Treatment | 4.99 | 0.4424 |
| Subjects (matching) | 12.2328 | 0.3063 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | ns | No |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 318.9 | 39.86 | 8.149 |
| Time | 2 | 6.178 | 3.089 | 0.6315 |
| Treatment | 4 | 25.5 | 6.376 | 1.02 |
| Subjects (matching) | 10 | 62.5 | 6.25 | 1.278 |
| Residual | 20 | 97.83 | 4.892 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.767 | 3.267 | -4.5 | -11.02 to 2.020 |
| 1 | 12.53 | 10.33 | -2.2 | -8.720 to 4.320 |
| 2 | 8.367 | 12.1 | 3.733 | -2.787 to 10.25 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -4.5 | 2.384 | P > 0.05 | ns |
| 1 | -2.2 | 1.166 | P > 0.05 | ns |
| 2 | 3.733 | 1.978 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.767 | 12.8 | 5.033 | -1.487 to 11.55 |
| 1 | 12.53 | 6.167 | -6.367 | -12.89 to 0.1536 |
| 2 | 8.367 | 10.67 | 2.3 | -4.220 to 8.820 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.033 | 2.667 | P < 0.05 | * |
| 1 | -6.367 | 3.373 | P<0.01 | ** |
| 2 | 2.3 | 1.219 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | | 7.767 | 13.37 | 5.6 | -0.9203 to 12.12 |
| 1 | | 12.53 | 9.467 | -3.067 | -9.587 to 3.454 |
| 2 | | 8.367 | 6.633 | -1.733 | -8.254 to 4.787 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.6 | 2.967 | P < 0.05 | * |
| 1 | -3.067 | 1.625 | P > 0.05 | ns |
| 2 | -1.733 | 0.9183 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 7.767 | 6.833 | -0.9333 | -7.454 to 5.587 |
| 1 | 12.53 | 9.867 | -2.667 | -9.187 to 3.854 |
| 2 | 8.367 | 7.267 | -1.1 | -7.620 to 5.420 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.9333 | 0.4945 | P > 0.05 | ns |
| 1 | -2.667 | 1.413 | P > 0.05 | ns |
| 2 | -1.1 | 0.5828 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.267 | 12.8 | 9.533 | 3.013 to 16.05 |
| 1 | 10.33 | 6.167 | -4.167 | -10.69 to 2.354 |
| 2 | 12.1 | 10.67 | -1.433 | -7.954 to 5.087 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 9.533 | 5.051 | P<0.001 | *** |
| 1 | -4.167 | 2.207 | P > 0.05 | ns |
| 2 | -1.433 | 0.7594 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.267 | 13.37 | 10.1 | 3.580 to 16.62 |
| 1 | 10.33 | 9.467 | -0.8667 | -7.387 to 5.654 |
| 2 | 12.1 | 6.633 | -5.467 | -11.99 to 1.054 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 10.1 | 5.351 | P<0.001 | *** |
| 1 | -0.8667 | 0.4592 | P > 0.05 | ns |
| 2 | -5.467 | 2.896 | P < 0.05 | * |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 3.267 | 6.833 | 3.567 | -2.954 to 10.09 |
| 1 | 10.33 | 9.867 | -0.4667 | -6.987 to 6.054 |
| 2 | 12.1 | 7.267 | -4.833 | -11.35 to 1.687 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 3.567 | 1.89 | P > 0.05 | ns |
| 1 | -0.4667 | 0.2472 | P > 0.05 | ns |
| 2 | -4.833 | 2.561 | P < 0.05 | * |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12.8 | 13.37 | 0.5667 | -5.954 to 7.087 |
| 1 | 6.167 | 9.467 | 3.3 | -3.220 to 9.820 |
| 2 | 10.67 | 6.633 | -4.033 | -10.55 to 2.487 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.5667 | 0.3002 | P > 0.05 | ns |
| 1 | 3.3 | 1.748 | P > 0.05 | ns |
| 2 | -4.033 | 2.137 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 12.8 | 6.833 | -5.967 | -12.49 to 0.5536 |
| 1 | 6.167 | 9.867 | 3.7 | -2.820 to 10.22 |
| 2 | 10.67 | 7.267 | -3.4 | -9.920 to 3.120 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -5.967 | 3.161 | P < 0.05 | * |
| 1 | 3.7 | 1.96 | P > 0.05 | ns |
| 2 | -3.4 | 1.801 | P > 0.05 | ns |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 13.37 | 6.833 | -6.533 | -13.05 to -0.01305 |
| 1 | 9.467 | 9.867 | 0.4 | -6.120 to 6.920 |
| 2 | 6.633 | 7.267 | 0.6333 | -5.887 to 7.154 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6.533 | 3.461 | P<0.01 | ** |
| 1 | 0.4 | 0.2119 | P > 0.05 | ns |
| 2 | 0.6333 | 0.3355 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 21.47 | 0.2324 |
| Time | 23.1 | 0.0076 |
| Treatment | 7.05 | 0.2714 |
| Subjects (matching) | 11.6627 | 0.7673 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 66.7 | 8.337 | 1.462 |
| Time | 2 | 71.76 | 35.88 | 6.292 |
| Treatment | 4 | 21.89 | 5.471 | 1.51 |
| Subjects (matching) | 10 | 36.23 | 3.623 | 0.6353 |
| Residual | 20 | 114 | 5.702 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5333 | 2 | 1.467 | -4.846 to 7.779 |
| 1 | 5.133 | 7.033 | 1.9 | -4.413 to 8.213 |
| 2 | 5.3 | 7.133 | 1.833 | -4.479 to 8.146 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.467 | 0.8026 | P > 0.05 | ns |
| 1 | 1.9 | 1.04 | P > 0.05 | ns |
| 2 | 1.833 | 1.003 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5333 | 4.567 | 4.033 | -2.279 to 10.35 |
| 1 | 5.133 | 4.3 | -0.8333 | -7.146 to 5.479 |
| 2 | 5.3 | 5.067 | -0.2333 | -6.546 to 6.079 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.033 | 2.207 | P > 0.05 | ns |
| 1 | -0.8333 | 0.456 | P > 0.05 | ns |
| 2 | -0.2333 | 0.1277 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | | 0.5333 | 4.433 | 3.9 | -2.413 to 10.21 |
| 1 | | 5.133 | 6.133 | 1 | -5.313 to 7.313 |
| 2 | | 5.3 | 3.533 | -1.767 | -8.079 to 4.546 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.9 | 2.134 | P > 0.05 | ns |
| 1 | 1 | 0.5472 | P > 0.05 | ns |
| 2 | -1.767 | 0.9668 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5333 | 2 | 1.467 | -4.846 to 7.779 |
| 1 | 5.133 | 6.167 | 1.033 | -5.279 to 7.346 |
| 2 | 5.3 | 2.433 | -2.867 | -9.179 to 3.446 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.467 | 0.8026 | P > 0.05 | ns |
| 1 | 1.033 | 0.5655 | P > 0.05 | ns |
| 2 | -2.867 | 1.569 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2 | 4.567 | 2.567 | -3.746 to 8.879 |
| 1 | 7.033 | 4.3 | -2.733 | -9.046 to 3.579 |
| 2 | 7.133 | 5.067 | -2.067 | -8.379 to 4.246 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.567 | 1.405 | P > 0.05 | ns |
| 1 | -2.733 | 1.496 | P > 0.05 | ns |
| 2 | -2.067 | 1.131 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2 | 4.433 | 2.433 | -3.879 to 8.746 |
| 1 | 7.033 | 6.133 | -0.9 | -7.213 to 5.413 |
| 2 | 7.133 | 3.533 | -3.6 | -9.913 to 2.713 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.433 | 1.332 | P > 0.05 | ns |
| 1 | -0.9 | 0.4925 | P > 0.05 | ns |
| 2 | -3.6 | 1.97 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2 | 2 | 0 | -6.313 to 6.313 |
| 1 | 7.033 | 6.167 | -0.8667 | -7.179 to 5.446 |
| 2 | 7.133 | 2.433 | -4.7 | -11.01 to 1.613 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0 | 0 | P > 0.05 | ns |
| 1 | -0.8667 | 0.4743 | P > 0.05 | ns |
| 2 | -4.7 | 2.572 | P < 0.05 | * |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.567 | 4.433 | -0.1333 | -6.446 to 6.179 |
| 1 | 4.3 | 6.133 | 1.833 | -4.479 to 8.146 |
| 2 | 5.067 | 3.533 | -1.533 | -7.846 to 4.779 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1333 | 0.07296 | P > 0.05 | ns |
| 1 | 1.833 | 1.003 | P > 0.05 | ns |
| 2 | -1.533 | 0.8391 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.567 | 2 | -2.567 | -8.879 to 3.746 |
| 1 | 4.3 | 6.167 | 1.867 | -4.446 to 8.179 |
| 2 | 5.067 | 2.433 | -2.633 | -8.946 to 3.679 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.567 | 1.405 | P > 0.05 | ns |
| 1 | 1.867 | 1.021 | P > 0.05 | ns |
| 2 | -2.633 | 1.441 | P > 0.05 | ns |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.433 | 2 | -2.433 | -8.746 to 3.879 |
| 1 | 6.133 | 6.167 | 0.03333 | -6.279 to 6.346 |
| 2 | 3.533 | 2.433 | -1.1 | -7.413 to 5.213 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.433 | 1.332 | P > 0.05 | ns |
| 1 | 0.03333 | 0.01824 | P > 0.05 | ns |
| 2 | -1.1 | 0.6019 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 31.48 | 0.0063 |
| Time | 37.26 | P<0.0001 |
| Treatment | 5.49 | 0.115 |
| Subjects (matching) | 5.6211 | 0.8282 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 241.9 | 30.24 | 3.906 |
| Time | 2 | 286.4 | 143.2 | 18.49 |
| Treatment | 4 | 42.19 | 10.55 | 2.442 |
| Subjects (matching) | 10 | 43.2 | 4.32 | 0.558 |
| Residual | 20 | 154.9 | 7.743 | |

Bonferroni posttests

Neo B 10-8 vs. Neo B 10-9

| Treatment | Neo B 10-8 | Neo B 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.233 | -1.767 | -6 | -13.25 to 1.247 |
| 1 | 0.1667 | 4.967 | 4.8 | -2.447 to 12.05 |
| 2 | 2.367 | 11.9 | 9.533 | 2.286 to 16.78 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -6 | 2.86 | P < 0.05 | * |
| 1 | 4.8 | 2.288 | P > 0.05 | ns |
| 2 | 9.533 | 4.544 | P<0.001 | *** |

Neo B 10-8 vs. Neo B 10-10

| Treatment | Neo B 10-8 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.233 | 1.833 | -2.4 | -9.647 to 4.847 |
| 1 | 0.1667 | 1.367 | 1.2 | -6.047 to 8.447 |
| 2 | 2.367 | 10.13 | 7.767 | 0.5197 to 15.01 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.4 | 1.144 | P > 0.05 | ns |
| 1 | 1.2 | 0.572 | P > 0.05 | ns |
| 2 | 7.767 | 3.702 | P<0.01 | ** |

Neo B 10-8 vs. Neo B 10-11

| Treatment | Neo B 10-8 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 4.233 | 1.533 | -2.7 | -9.947 to 4.547 |
| 1 | 0.1667 | 5.167 | 5 | -2.247 to 12.25 |
| 2 | 2.367 | 7.233 | 4.867 | -2.380 to 12.11 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.7 | 1.287 | P > 0.05 | ns |
| 1 | 5 | 2.383 | P > 0.05 | ns |
| 2 | 4.867 | 2.32 | P > 0.05 | ns |

Neo B 10-8 vs. Neo B 10-12

| Treatment | Neo B 10-8 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 4.233 | 1.767 | -2.467 | -9.714 to 4.780 |
| 1 | 0.1667 | 4.533 | 4.367 | -2.880 to 11.61 |
| 2 | 2.367 | 5.967 | 3.6 | -3.647 to 10.85 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -2.467 | 1.176 | P > 0.05 | ns |
| 1 | 4.367 | 2.081 | P > 0.05 | ns |
| 2 | 3.6 | 1.716 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-10

| Treatment | Neo B 10-9 | Neo B 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.767 | 1.833 | 3.6 | -3.647 to 10.85 |
| 1 | 4.967 | 1.367 | -3.6 | -10.85 to 3.647 |
| 2 | 11.9 | 10.13 | -1.767 | -9.014 to 5.480 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.6 | 1.716 | P > 0.05 | ns |
| 1 | -3.6 | 1.716 | P > 0.05 | ns |
| 2 | -1.767 | 0.8421 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-11

| Treatment | Neo B 10-9 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.767 | 1.533 | 3.3 | -3.947 to 10.55 |
| 1 | 4.967 | 5.167 | 0.2 | -7.047 to 7.447 |
| 2 | 11.9 | 7.233 | -4.667 | -11.91 to 2.580 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.3 | 1.573 | P > 0.05 | ns |
| 1 | 0.2 | 0.09533 | P > 0.05 | ns |
| 2 | -4.667 | 2.224 | P > 0.05 | ns |

Neo B 10-9 vs. Neo B 10-12

| Treatment | Neo B 10-9 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.767 | 1.767 | 3.533 | -3.714 to 10.78 |
| 1 | 4.967 | 4.533 | -0.4333 | -7.680 to 6.814 |
| 2 | 11.9 | 5.967 | -5.933 | -13.18 to 1.314 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 3.533 | 1.684 | P > 0.05 | ns |
| 1 | -0.4333 | 0.2066 | P > 0.05 | ns |
| 2 | -5.933 | 2.828 | P < 0.05 | * |

Neo B 10-10 vs. Neo B 10-11

| Treatment | Neo B 10-10 | Neo B 10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.833 | 1.533 | -0.3 | -7.547 to 6.947 |
| 1 | 1.367 | 5.167 | 3.8 | -3.447 to 11.05 |
| 2 | 10.13 | 7.233 | -2.9 | -10.15 to 4.347 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.3 | 0.143 | P > 0.05 | ns |
| 1 | 3.8 | 1.811 | P > 0.05 | ns |
| 2 | -2.9 | 1.382 | P > 0.05 | ns |

Neo B 10-10 vs. Neo B 10-12

| Treatment | Neo B 10-10 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.833 | 1.767 | -0.06667 | -7.314 to 7.180 |
| 1 | 1.367 | 4.533 | 3.167 | -4.080 to 10.41 |
| 2 | 10.13 | 5.967 | -4.167 | -11.41 to 3.080 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.06667 | 0.03178 | P > 0.05 | ns |
| 1 | 3.167 | 1.509 | P > 0.05 | ns |
| 2 | -4.167 | 1.986 | P > 0.05 | ns |

Neo B 10-11 vs. Neo B 10-12

| Treatment | Neo B 10-11 | Neo B 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.533 | 1.767 | 0.2333 | -7.014 to 7.480 |
| 1 | 5.167 | 4.533 | -0.6333 | -7.880 to 6.614 |
| 2 | 7.233 | 5.967 | -1.267 | -8.514 to 5.980 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2333 | 0.1112 | P > 0.05 | ns |
| 1 | -0.6333 | 0.3019 | P > 0.05 | ns |
| 2 | -1.267 | 0.6038 | P > 0.05 | ns |

APPENDIX VII – ANOVA TABLES Glucan Dose Dependence

| | |
|---|---|
| Table Analyzed | Bmp2 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 9.92 | 0.2182 |
| Time | 45 | P<0.0001 |
| Treatment | 15.5 | 0.0745 |
| Subjects (matching) | 13.0776 | 0.1827 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | *** | Yes |
| Treatment | ns | No |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 37.21 | 4.651 | 1.502 |
| Time | 2 | 168.8 | 84.39 | 27.26 |
| Treatment | 4 | 58.14 | 14.54 | 2.963 |
| Subjects (matching) | 10 | 49.06 | 4.906 | 1.585 |
| Residual | 20 | 61.92 | 3.096 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -2.967 | -3.067 | -0.1 | -5.525 to 5.325 |
| 1 | -5.633 | -2.833 | 2.8 | -2.625 to 8.225 |
| 2 | 2.2 | 1.033 | -1.167 | -6.591 to 4.258 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1 | 0.06368 | P > 0.05 | ns |
| 1 | 2.8 | 1.783 | P > 0.05 | ns |
| 2 | -1.167 | 0.7429 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -2.967 | -0.8 | 2.167 | -3.258 to 7.591 |
| 1 | -5.633 | -0.3333 | 5.3 | -0.1247 to 10.72 |
| 2 | 2.2 | 1.4 | -0.8 | -6.225 to 4.625 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.167 | 1.38 | P > 0.05 | ns |
| 1 | 5.3 | 3.375 | P<0.01 | ** |
| 2 | -0.8 | 0.5094 | P > 0.05 | ns |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -2.967 | -1.1 | 1.867 | -3.558 to 7.291 |
| 1 | -5.633 | -2.233 | 3.4 | -2.025 to 8.825 |
| 2 | 2.2 | 1 | -1.2 | -6.625 to 4.225 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.867 | 1.189 | P > 0.05 | ns |
| 1 | 3.4 | 2.165 | P > 0.05 | ns |
| 2 | -1.2 | 0.7641 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -2.967 | -0.6667 | 2.3 | -3.125 to 7.725 |
| 1 | -5.633 | -0.8 | 4.833 | -0.5913 to 10.26 |
| 2 | 2.2 | 4.5 | 2.3 | -3.125 to 7.725 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.3 | 1.465 | P > 0.05 | ns |
| 1 | 4.833 | 3.078 | P < 0.05 | * |
| 2 | 2.3 | 1.465 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.067 | -0.8 | 2.267 | -3.158 to 7.691 |
| 1 | -2.833 | -0.3333 | 2.5 | -2.925 to 7.925 |
| 2 | 1.033 | 1.4 | 0.3667 | -5.058 to 5.791 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.267 | 1.443 | P > 0.05 | ns |
| 1 | 2.5 | 1.592 | P > 0.05 | ns |
| 2 | 0.3667 | 0.2335 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.067 | -1.1 | 1.967 | -3.458 to 7.391 |
| 1 | -2.833 | -2.233 | 0.6 | -4.825 to 6.025 |
| 2 | 1.033 | 1 | -0.03333 | -5.458 to 5.391 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.967 | 1.252 | P > 0.05 | ns |
| 1 | 0.6 | 0.3821 | P > 0.05 | ns |
| 2 | -0.03333 | 0.02123 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.067 | -0.6667 | 2.4 | -3.025 to 7.825 |
| 1 | -2.833 | -0.8 | 2.033 | -3.391 to 7.458 |
| 2 | 1.033 | 4.5 | 3.467 | -1.958 to 8.891 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.4 | 1.528 | P > 0.05 | ns |
| 1 | 2.033 | 1.295 | P > 0.05 | ns |
| 2 | 3.467 | 2.208 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.8 | -1.1 | -0.3 | -5.725 to 5.125 |
| 1 | -0.3333 | -2.233 | -1.9 | -7.325 to 3.525 |
| 2 | 1.4 | 1 | -0.4 | -5.825 to 5.025 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.3 | 0.191 | P > 0.05 | ns |
| 1 | -1.9 | 1.21 | P > 0.05 | ns |
| 2 | -0.4 | 0.2547 | P > 0.05 | ns |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.8 | -0.6667 | 0.1333 | -5.291 to 5.558 |
| 1 | -0.3333 | -0.8 | -0.4667 | -5.891 to 4.958 |
| 2 | 1.4 | 4.5 | 3.1 | -2.325 to 8.525 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.1333 | 0.08491 | P > 0.05 | ns |
| 1 | -0.4667 | 0.2972 | P > 0.05 | ns |
| 2 | 3.1 | 1.974 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.1 | -0.6667 | 0.4333 | -4.991 to 5.858 |
| 1 | -2.233 | -0.8 | 1.433 | -3.991 to 6.858 |
| 2 | 1 | 4.5 | 3.5 | -1.925 to 8.925 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.4333 | 0.2759 | P > 0.05 | ns |
| 1 | 1.433 | 0.9127 | P > 0.05 | ns |
| 2 | 3.5 | 2.229 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Hspb1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 6.79 | 0.5873 |
| Time | 12.47 | 0.0086 |
| Treatment | 38.06 | 0.0282 |
| Subjects (matching) | 22.2082 | 0.0673 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ns | No |
| Time | ** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 19.57 | 2.447 | 0.8294 |
| Time | 2 | 35.96 | 17.98 | 6.095 |
| Treatment | 4 | 109.7 | 27.43 | 4.285 |
| Subjects (matching) | 10 | 64.02 | 6.402 | 2.17 |
| Residual | 20 | 59 | 2.95 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.633 | 0.5667 | 4.2 | -1.512 to 9.912 |
| 1 | -0.7 | 1.4 | 2.1 | -3.612 to 7.812 |
| 2 | 0.3667 | 0.4667 | 0.1 | -5.612 to 5.812 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.2 | 2.54 | P < 0.05 | * |
| 1 | 2.1 | 1.27 | P > 0.05 | ns |
| 2 | 0.1 | 0.06048 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.633 | 0.3667 | 4 | -1.712 to 9.712 |
| 1 | -0.7 | 1.233 | 1.933 | -3.778 to 7.645 |
| 2 | 0.3667 | 1.533 | 1.167 | -4.545 to 6.878 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4 | 2.419 | P > 0.05 | ns |
| 1 | 1.933 | 1.169 | P > 0.05 | ns |
| 2 | 1.167 | 0.7056 | P > 0.05 | ns |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | | -3.633 | -0.03333 | 3.6 | -2.112 to 9.312 |
| 1 | | -0.7 | 2.833 | 3.533 | -2.178 to 9.245 |
| 2 | | 0.3667 | 1.133 | 0.7667 | -4.945 to 6.478 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.6 | 2.177 | P > 0.05 | ns |
| 1 | 3.533 | 2.137 | P > 0.05 | ns |
| 2 | 0.7667 | 0.4637 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.633 | 1.867 | 5.5 | -0.2117 to 11.21 |
| 1 | -0.7 | 4.267 | 4.967 | -0.7450 to 10.68 |
| 2 | 0.3667 | 4.633 | 4.267 | -1.445 to 9.978 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 5.5 | 3.326 | P<0.01 | ** |
| 1 | 4.967 | 3.004 | P < 0.05 | * |
| 2 | 4.267 | 2.58 | P < 0.05 | * |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5667 | 0.3667 | -0.2 | -5.912 to 5.512 |
| 1 | 1.4 | 1.233 | -0.1667 | -5.878 to 5.545 |
| 2 | 0.4667 | 1.533 | 1.067 | -4.645 to 6.778 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.2 | 0.121 | P > 0.05 | ns |
| 1 | -0.1667 | 0.1008 | P > 0.05 | ns |
| 2 | 1.067 | 0.6451 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5667 | -0.03333 | -0.6 | -6.312 to 5.112 |
| 1 | 1.4 | 2.833 | 1.433 | -4.278 to 7.145 |
| 2 | 0.4667 | 1.133 | 0.6667 | -5.045 to 6.378 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.6 | 0.3629 | P > 0.05 | ns |
| 1 | 1.433 | 0.8669 | P > 0.05 | ns |
| 2 | 0.6667 | 0.4032 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.5667 | 1.867 | 1.3 | -4.412 to 7.012 |
| 1 | 1.4 | 4.267 | 2.867 | -2.845 to 8.578 |
| 2 | 0.4667 | 4.633 | 4.167 | -1.545 to 9.878 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 1.3 | 0.7862 | P > 0.05 | ns |
| 1 | 2.867 | 1.734 | P > 0.05 | ns |
| 2 | 4.167 | 2.52 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.3667 | -0.03333 | -0.4 | -6.112 to 5.312 |
| 1 | 1.233 | 2.833 | 1.6 | -4.112 to 7.312 |
| 2 | 1.533 | 1.133 | -0.4 | -6.112 to 5.312 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4 | 0.2419 | P > 0.05 | ns |
| 1 | 1.6 | 0.9677 | P > 0.05 | ns |
| 2 | -0.4 | 0.2419 | P > 0.05 | ns |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.3667 | 1.867 | 1.5 | -4.212 to 7.212 |
| 1 | 1.233 | 4.267 | 3.033 | -2.678 to 8.745 |
| 2 | 1.533 | 4.633 | 3.1 | -2.612 to 8.812 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.5 | 0.9072 | P > 0.05 | ns |
| 1 | 3.033 | 1.835 | P > 0.05 | ns |
| 2 | 3.1 | 1.875 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.03333 | 1.867 | 1.9 | -3.812 to 7.612 |
| 1 | 2.833 | 4.267 | 1.433 | -4.278 to 7.145 |
| 2 | 1.133 | 4.633 | 3.5 | -2.212 to 9.212 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.9 | 1.149 | P > 0.05 | ns |
| 1 | 1.433 | 0.8669 | P > 0.05 | ns |
| 2 | 3.5 | 2.117 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Icam1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 34.73 | 0.0008 |
| Time | 16.21 | 0.0007 |
| Treatment | 26.38 | 0.0025 |
| Subjects (matching) | 7.4059 | 0.4973 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | *** | Yes |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 130.9 | 16.36 | 5.685 |
| Time | 2 | 61.09 | 30.54 | 10.61 |
| Treatment | 4 | 99.43 | 24.86 | 8.906 |
| Subjects (matching) | 10 | 27.91 | 2.791 | 0.9699 |
| Residual | 20 | 57.56 | 2.878 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.5 | -1.067 | 2.433 | -2.327 to 7.194 |
| 1 | -8.6 | 0.8667 | 9.467 | 4.706 to 14.23 |
| 2 | 1.6 | 1 | -0.6 | -5.361 to 4.161 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.433 | 1.766 | P > 0.05 | ns |
| 1 | 9.467 | 6.869 | P<0.001 | *** |
| 2 | -0.6 | 0.4354 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.5 | -0.4 | 3.1 | -1.661 to 7.861 |
| 1 | -8.6 | -0.1667 | 8.433 | 3.673 to 13.19 |
| 2 | 1.6 | 1.833 | 0.2333 | -4.527 to 4.994 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.1 | 2.249 | P > 0.05 | ns |
| 1 | 8.433 | 6.119 | P<0.001 | *** |
| 2 | 0.2333 | 0.1693 | P > 0.05 | ns |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | -3.5 | -1 | 2.5 | -2.261 to 7.261 |
| 1 | -8.6 | 0.9 | 9.5 | 4.739 to 14.26 |
| 2 | 1.6 | -1 | -2.6 | -7.361 to 2.161 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.5 | 1.814 | P > 0.05 | ns |
| 1 | 9.5 | 6.893 | P<0.001 | *** |
| 2 | -2.6 | 1.887 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.5 | -0.2333 | 3.267 | -1.494 to 8.027 |
| 1 | -8.6 | -0.7667 | 7.833 | 3.073 to 12.59 |
| 2 | 1.6 | 1.867 | 0.2667 | -4.494 to 5.027 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.267 | 2.37 | P > 0.05 | ns |
| 1 | 7.833 | 5.684 | P<0.001 | *** |
| 2 | 0.2667 | 0.1935 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.067 | -0.4 | 0.6667 | -4.094 to 5.427 |
| 1 | 0.8667 | -0.1667 | -1.033 | -5.794 to 3.727 |
| 2 | 1 | 1.833 | 0.8333 | -3.927 to 5.594 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6667 | 0.4837 | P > 0.05 | ns |
| 1 | -1.033 | 0.7498 | P > 0.05 | ns |
| 2 | 0.8333 | 0.6047 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.067 | -1 | 0.06667 | -4.694 to 4.827 |
| 1 | 0.8667 | 0.9 | 0.03333 | -4.727 to 4.794 |
| 2 | 1 | -1 | -2 | -6.761 to 2.761 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.06667 | 0.04837 | P > 0.05 | ns |
| 1 | 0.03333 | 0.02419 | P > 0.05 | ns |
| 2 | -2 | 1.451 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.067 | -0.2333 | 0.8333 | -3.927 to 5.594 |
| 1 | 0.8667 | -0.7667 | -1.633 | -6.394 to 3.127 |
| 2 | 1 | 1.867 | 0.8667 | -3.894 to 5.627 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0.8333 | 0.6047 | P > 0.05 | ns |
| 1 | -1.633 | 1.185 | P > 0.05 | ns |
| 2 | 0.8667 | 0.6289 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.4 | -1 | -0.6 | -5.361 to 4.161 |
| 1 | -0.1667 | 0.9 | 1.067 | -3.694 to 5.827 |
| 2 | 1.833 | -1 | -2.833 | -7.594 to 1.927 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.6 | 0.4354 | P > 0.05 | ns |
| 1 | 1.067 | 0.774 | P > 0.05 | ns |
| 2 | -2.833 | 2.056 | P > 0.05 | ns |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.4 | -0.2333 | 0.1667 | -4.594 to 4.927 |
| 1 | -0.1667 | -0.7667 | -0.6 | -5.361 to 4.161 |
| 2 | 1.833 | 1.867 | 0.03333 | -4.727 to 4.794 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.1667 | 0.1209 | P > 0.05 | ns |
| 1 | -0.6 | 0.4354 | P > 0.05 | ns |
| 2 | 0.03333 | 0.02419 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1 | -0.2333 | 0.7667 | -3.994 to 5.527 |
| 1 | 0.9 | -0.7667 | -1.667 | -6.427 to 3.094 |
| 2 | -1 | 1.867 | 2.867 | -1.894 to 7.627 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7667 | 0.5563 | P > 0.05 | ns |
| 1 | -1.667 | 1.209 | P > 0.05 | ns |
| 2 | 2.867 | 2.08 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Vegfa |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 23.92 | 0.016 |
| Time | 37.67 | P<0.0001 |
| Treatment | 11.56 | 0.0498 |
| Subjects (matching) | 8.2923 | 0.5552 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | *** | Yes |
| Treatment | * | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 110.5 | 13.81 | 3.223 |
| Time | 2 | 174 | 87.02 | 20.3 |
| Treatment | 4 | 53.4 | 13.35 | 3.485 |
| Subjects (matching) | 10 | 38.31 | 3.831 | 0.8938 |
| Residual | 20 | 85.72 | 4.286 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.8 | 0.2667 | 4.067 | -1.668 to 9.802 |
| 1 | -3.633 | 0.9 | 4.533 | -1.202 to 10.27 |
| 2 | 5.2 | 3.433 | -1.767 | -7.502 to 3.968 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.067 | 2.449 | P > 0.05 | ns |
| 1 | 4.533 | 2.731 | P < 0.05 | * |
| 2 | -1.767 | 1.064 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.8 | 0.1667 | 3.967 | -1.768 to 9.702 |
| 1 | -3.633 | 0.6 | 4.233 | -1.502 to 9.968 |
| 2 | 5.2 | 2.767 | -2.433 | -8.168 to 3.302 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.967 | 2.389 | P > 0.05 | ns |
| 1 | 4.233 | 2.55 | P < 0.05 | * |
| 2 | -2.433 | 1.466 | P > 0.05 | ns |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 0.5 | -3.8 | -0.2333 | 3.567 | -2.168 to 9.302 | |
| 1 | -3.633 | -3.2 | 0.4333 | -5.302 to 6.168 | |
| 2 | 5.2 | -0.2333 | -5.433 | -11.17 to 0.3017 | |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.567 | 2.148 | P > 0.05 | ns |
| 1 | 0.4333 | 0.261 | P > 0.05 | ns |
| 2 | -5.433 | 3.273 | P<0.01 | ** |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -3.8 | 0.8 | 4.6 | -1.135 to 10.33 |
| 1 | -3.633 | -4.5 | -0.8667 | -6.602 to 4.868 |
| 2 | 5.2 | 2.467 | -2.733 | -8.468 to 3.002 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.6 | 2.771 | P < 0.05 | * |
| 1 | -0.8667 | 0.522 | P > 0.05 | ns |
| 2 | -2.733 | 1.646 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.2667 | 0.1667 | -0.1 | -5.835 to 5.635 |
| 1 | 0.9 | 0.6 | -0.3 | -6.035 to 5.435 |
| 2 | 3.433 | 2.767 | -0.6667 | -6.402 to 5.068 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.1 | 0.06023 | P > 0.05 | ns |
| 1 | -0.3 | 0.1807 | P > 0.05 | ns |
| 2 | -0.6667 | 0.4016 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.2667 | -0.2333 | -0.5 | -6.235 to 5.235 |
| 1 | 0.9 | -3.2 | -4.1 | -9.835 to 1.635 |
| 2 | 3.433 | -0.2333 | -3.667 | -9.402 to 2.068 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5 | 0.3012 | P > 0.05 | ns |
| 1 | -4.1 | 2.47 | P > 0.05 | ns |
| 2 | -3.667 | 2.209 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.2667 | 0.8 | 0.5333 | -5.202 to 6.268 |
| 1 | 0.9 | -4.5 | -5.4 | -11.13 to 0.3350 |
| 2 | 3.433 | 2.467 | -0.9667 | -6.702 to 4.768 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0.5333 | 0.3212 | P > 0.05 | ns |
| 1 | -5.4 | 3.253 | P<0.01 | ** |
| 2 | -0.9667 | 0.5823 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.1667 | -0.2333 | -0.4 | -6.135 to 5.335 |
| 1 | 0.6 | -3.2 | -3.8 | -9.535 to 1.935 |
| 2 | 2.767 | -0.2333 | -3 | -8.735 to 2.735 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4 | 0.2409 | P > 0.05 | ns |
| 1 | -3.8 | 2.289 | P > 0.05 | ns |
| 2 | -3 | 1.807 | P > 0.05 | ns |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.1667 | 0.8 | 0.6333 | -5.102 to 6.368 |
| 1 | 0.6 | -4.5 | -5.1 | -10.83 to 0.6350 |
| 2 | 2.767 | 2.467 | -0.3 | -6.035 to 5.435 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6333 | 0.3815 | P > 0.05 | ns |
| 1 | -5.1 | 3.072 | P < 0.05 | * |
| 2 | -0.3 | 0.1807 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.2333 | 0.8 | 1.033 | -4.702 to 6.768 |
| 1 | -3.2 | -4.5 | -1.3 | -7.035 to 4.435 |
| 2 | -0.2333 | 2.467 | 2.7 | -3.035 to 8.435 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.033 | 0.6224 | P > 0.05 | ns |
| 1 | -1.3 | 0.783 | P > 0.05 | ns |
| 2 | 2.7 | 1.626 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Cdknlb |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 12.15 | 0.0289 |
| Time | 43.77 | P<0.0001 |
| Treatment | 28.34 | 0.0004 |
| Subjects (matching) | 4.9385 | 0.539 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | * | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 66.75 | 8.343 | 2.813 |
| Time | 2 | 240.4 | 120.2 | 40.53 |
| Treatment | 4 | 155.7 | 38.92 | 14.35 |
| Subjects (matching) | 10 | 27.13 | 2.713 | 0.9146 |
| Residual | 20 | 59.32 | 2.966 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -4.067 | -0.2 | 3.867 | -0.9211 to 8.654 |
| 1 | -8.133 | 0.2333 | 8.367 | 3.579 to 13.15 |
| 2 | 1.633 | 4.767 | 3.133 | -1.654 to 7.921 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.867 | 2.79 | P < 0.05 | * |
| 1 | 8.367 | 6.036 | P<0.001 | *** |
| 2 | 3.133 | 2.261 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -4.067 | -0.7 | 3.367 | -1.421 to 8.154 |
| 1 | -8.133 | 0.2333 | 8.367 | 3.579 to 13.15 |
| 2 | 1.633 | 4.133 | 2.5 | -2.288 to 7.288 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.367 | 2.429 | P > 0.05 | ns |
| 1 | 8.367 | 6.036 | P<0.001 | *** |
| 2 | 2.5 | 1.804 | P > 0.05 | ns |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -4.067 | 0.1333 | 4.2 | -0.5878 to 8.988 |
| 1 | -8.133 | -2.167 | 5.967 | 1.179 to 10.75 |
| 2 | 1.633 | 0.5333 | -1.1 | -5.888 to 3.688 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.2 | 3.03 | P < 0.05 | * |
| 1 | 5.967 | 4.305 | P<0.001 | *** |
| 2 | -1.1 | 0.7936 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -4.067 | 0.4667 | 4.533 | -0.2545 to 9.321 |
| 1 | -8.133 | -2.333 | 5.8 | 1.012 to 10.59 |
| 2 | 1.633 | 4.233 | 2.6 | -2.188 to 7.388 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.533 | 3.271 | P<0.01 | ** |
| 1 | 5.8 | 4.185 | P<0.001 | *** |
| 2 | 2.6 | 1.876 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.2 | -0.7 | -0.5 | -5.288 to 4.288 |
| 1 | 0.2333 | 0.2333 | 0 | -4.788 to 4.788 |
| 2 | 4.767 | 4.133 | -0.6333 | -5.421 to 4.154 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5 | 0.3607 | P > 0.05 | ns |
| 1 | 0 | 0 | P > 0.05 | ns |
| 2 | -0.6333 | 0.4569 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.2 | 0.1333 | 0.3333 | -4.454 to 5.121 |
| 1 | 0.2333 | -2.167 | -2.4 | -7.188 to 2.388 |
| 2 | 4.767 | 0.5333 | -4.233 | -9.021 to 0.5545 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.3333 | 0.2405 | P > 0.05 | ns |
| 1 | -2.4 | 1.732 | P > 0.05 | ns |
| 2 | -4.233 | 3.054 | P < 0.05 | * |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.2 | 0.4667 | 0.6667 | -4.121 to 5.454 |
| 1 | 0.2333 | -2.333 | -2.567 | -7.354 to 2.221 |
| 2 | 4.767 | 4.233 | -0.5333 | -5.321 to 4.254 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6667 | 0.481 | P > 0.05 | ns |
| 1 | -2.567 | 1.852 | P > 0.05 | ns |
| 2 | -0.5333 | 0.3848 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.7 | 0.1333 | 0.8333 | -3.954 to 5.621 |
| 1 | 0.2333 | -2.167 | -2.4 | -7.188 to 2.388 |
| 2 | 4.133 | 0.5333 | -3.6 | -8.388 to 1.188 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.8333 | 0.6012 | P > 0.05 | ns |
| 1 | -2.4 | 1.732 | P > 0.05 | ns |
| 2 | -3.6 | 2.597 | P < 0.05 | * |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -0.7 | 0.4667 | 1.167 | -3.621 to 5.954 |
| 1 | 0.2333 | -2.333 | -2.567 | -7.354 to 2.221 |
| 2 | 4.133 | 4.233 | 0.1 | -4.688 to 4.888 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.167 | 0.8417 | P > 0.05 | ns |
| 1 | -2.567 | 1.852 | P > 0.05 | ns |
| 2 | 0.1 | 0.07215 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.1333 | 0.4667 | 0.3333 | -4.454 to 5.121 |
| 1 | -2.167 | -2.333 | -0.1667 | -4.954 to 4.621 |
| 2 | 0.5333 | 4.233 | 3.7 | -1.088 to 8.488 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.3333 | 0.2405 | P > 0.05 | ns |
| 1 | -0.1667 | 0.1202 | P > 0.05 | ns |
| 2 | 3.7 | 2.67 | P < 0.05 | * |

| | |
|---|---|
| Table Analyzed | Cd5 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 18.97 | 0.0079 |
| Time | 1.19 | 0.4088 |
| Treatment | 54.2 | 0.0013 |
| Subjects (matching) | 12.9644 | 0.083 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | ** | Yes |
| Time | ns | No |
| Treatment | ** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 57.38 | 7.172 | 3.743 |
| Time | 2 | 3.586 | 1.793 | 0.9358 |
| Treatment | 4 | 163.9 | 40.98 | 10.45 |
| Subjects (matching) | 10 | 39.2 | 3.92 | 2.046 |
| Residual | 20 | 38.32 | 1.916 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.633 | 1.467 | 3.1 | -1.434 to 7.634 |
| 1 | -1.167 | 0.2 | 1.367 | -3.167 to 5.901 |
| 2 | -1.333 | 2.1 | 3.433 | -1.101 to 7.967 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.1 | 2.362 | P > 0.05 | ns |
| 1 | 1.367 | 1.041 | P > 0.05 | ns |
| 2 | 3.433 | 2.616 | P < 0.05 | * |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.633 | 2.467 | 4.1 | -0.4339 to 8.634 |
| 1 | -1.167 | 0.1667 | 1.333 | -3.201 to 5.867 |
| 2 | -1.333 | 3.067 | 4.4 | -0.1339 to 8.934 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.1 | 3.124 | P < 0.05 | * |
| 1 | 1.333 | 1.016 | P > 0.05 | ns |
| 2 | 4.4 | 3.352 | P<0.01 | ** |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | -1.633 | 1.9 | 3.533 | -1.001 to 8.067 |
| 1 | -1.167 | 5.9 | 7.067 | 2.533 to 11.60 |
| 2 | -1.333 | 1.667 | 3 | -1.534 to 7.534 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 3.533 | 2.692 | P < 0.05 | * |
| 1 | 7.067 | 5.384 | P<0.001 | *** |
| 2 | 3 | 2.286 | P > 0.05 | ns |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | -1.633 | 3 | 4.633 | 0.09945 to 9.167 |
| 1 | -1.167 | 4.833 | 6 | 1.466 to 10.53 |
| 2 | -1.333 | 4.9 | 6.233 | 1.699 to 10.77 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 4.633 | 3.53 | P<0.01 | ** |
| 1 | 6 | 4.571 | P<0.001 | *** |
| 2 | 6.233 | 4.749 | P<0.001 | *** |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.467 | 2.467 | 1 | -3.534 to 5.534 |
| 1 | 0.2 | 0.1667 | -0.03333 | -4.567 to 4.501 |
| 2 | 2.1 | 3.067 | 0.9667 | -3.567 to 5.501 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1 | 0.7619 | P > 0.05 | ns |
| 1 | -0.03333 | 0.0254 | P > 0.05 | ns |
| 2 | 0.9667 | 0.7365 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.467 | 1.9 | 0.4333 | -4.101 to 4.967 |
| 1 | 0.2 | 5.9 | 5.7 | 1.166 to 10.23 |
| 2 | 2.1 | 1.667 | -0.4333 | -4.967 to 4.101 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.4333 | 0.3302 | P > 0.05 | ns |
| 1 | 5.7 | 4.343 | P<0.001 | *** |
| 2 | -0.4333 | 0.3302 | P > 0.05 | ns |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.467 | 3 | 1.533 | -3.001 to 6.067 |
| 1 | 0.2 | 4.833 | 4.633 | 0.09945 to 9.167 |
| 2 | 2.1 | 4.9 | 2.8 | -1.734 to 7.334 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.533 | 1.168 | P > 0.05 | ns |
| 1 | 4.633 | 3.53 | P<0.01 | ** |
| 2 | 2.8 | 2.133 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.467 | 1.9 | -0.5667 | -5.101 to 3.967 |
| 1 | 0.1667 | 5.9 | 5.733 | 1.199 to 10.27 |
| 2 | 3.067 | 1.667 | -1.4 | -5.934 to 3.134 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.5667 | 0.4317 | P > 0.05 | ns |
| 1 | 5.733 | 4.368 | P<0.001 | *** |
| 2 | -1.4 | 1.067 | P > 0.05 | ns |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 2.467 | 3 | 0.5333 | -4.001 to 5.067 |
| 1 | 0.1667 | 4.833 | 4.667 | 0.1328 to 9.201 |
| 2 | 3.067 | 4.9 | 1.833 | -2.701 to 6.367 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.5333 | 0.4063 | P > 0.05 | ns |
| 1 | 4.667 | 3.556 | P<0.01 | ** |
| 2 | 1.833 | 1.397 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.9 | 3 | 1.1 | -3.434 to 5.634 |
| 1 | 5.9 | 4.833 | -1.067 | -5.601 to 3.467 |
| 2 | 1.667 | 4.9 | 3.233 | -1.301 to 7.767 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.1 | 0.8381 | P > 0.05 | ns |
| 1 | -1.067 | 0.8127 | P > 0.05 | ns |
| 2 | 3.233 | 2.463 | P > 0.05 | ns |

| | |
|---|---|
| Table Analyzed | Dectin-1 |
| Two-way RM ANOVA | Matching by cols |

| Source of Variation | % of total variation | P value |
|---|---|---|
| Interaction | 16.77 | P<0.0001 |
| Time | 37.15 | P<0.0001 |
| Treatment | 37.8 | P<0.0001 |
| Subjects (matching) | 3.6199 | 0.1925 |

| Source of Variation | P value summary | Significant? |
|---|---|---|
| Interaction | *** | Yes |
| Time | *** | Yes |
| Treatment | *** | Yes |
| Subjects (matching) | ns | No |

| Source of Variation | Df | Sum-of-squares | Mean square | F |
|---|---|---|---|---|
| Interaction | 8 | 111 | 13.88 | 8.995 |
| Time | 2 | 246 | 123 | 79.73 |
| Treatment | 4 | 250.3 | 62.56 | 26.11 |
| Subjects (matching) | 10 | 23.96 | 2.396 | 1.554 |
| Residual | 20 | 30.85 | 1.542 | |

Bonferroni posttests

glucan 10-8 vs. glucan 10-9

| Treatment | glucan 10-8 | glucan 10-9 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.2667 | 1.3 | 1.033 | -2.779 to 4.846 |
| 1 | 0.1333 | 5.9 | 5.767 | 1.954 to 9.579 |
| 2 | -8.767 | 2.333 | 11.1 | 7.288 to 14.91 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.033 | 0.9363 | P > 0.05 | ns |
| 1 | 5.767 | 5.225 | P<0.001 | *** |
| 2 | 11.1 | 10.06 | P<0.001 | *** |

glucan 10-8 vs. glucan 10-10

| Treatment | glucan 10-8 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.2667 | 1.933 | 1.667 | -2.146 to 5.479 |
| 1 | 0.1333 | 6.467 | 6.333 | 2.521 to 10.15 |
| 2 | -8.767 | 2.667 | 11.43 | 7.621 to 15.25 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.667 | 1.51 | P > 0.05 | ns |
| 1 | 6.333 | 5.738 | P<0.001 | *** |
| 2 | 11.43 | 10.36 | P<0.001 | *** |

glucan 10-8 vs. glucan10-11

| Treatment | glucan 10-8 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 0.2667 | 1.533 | 1.267 | -2.546 to 5.079 |
| 1 | 0.1333 | 5.5 | 5.367 | 1.554 to 9.179 |
| 2 | -8.767 | -2.6 | 6.167 | 2.354 to 9.979 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.267 | 1.148 | P > 0.05 | ns |
| 1 | 5.367 | 4.863 | P<0.001 | *** |
| 2 | 6.167 | 5.587 | P<0.001 | *** |

glucan 10-8 vs. glucan 10-12

| Treatment | glucan 10-8 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 0.2667 | 2.633 | 2.367 | -1.446 to 6.179 |
| 1 | 0.1333 | 5.167 | 5.033 | 1.221 to 8.846 |
| 2 | -8.767 | 0.9333 | 9.7 | 5.888 to 13.51 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 2.367 | 2.144 | P > 0.05 | ns |
| 1 | 5.033 | 4.561 | P<0.001 | *** |
| 2 | 9.7 | 8.789 | P<0.001 | *** |

glucan 10-9 vs. glucan 10-10

| Treatment | glucan 10-9 | glucan 10-10 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.3 | 1.933 | 0.6333 | -3.179 to 4.446 |
| 1 | 5.9 | 6.467 | 0.5667 | -3.246 to 4.379 |
| 2 | 2.333 | 2.667 | 0.3333 | -3.479 to 4.146 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.6333 | 0.5738 | P > 0.05 | ns |
| 1 | 0.5667 | 0.5134 | P > 0.05 | ns |
| 2 | 0.3333 | 0.302 | P > 0.05 | ns |

glucan 10-9 vs. glucan10-11

| Treatment | glucan 10-9 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.3 | 1.533 | 0.2333 | -3.579 to 4.046 |
| 1 | 5.9 | 5.5 | -0.4 | -4.212 to 3.412 |
| 2 | 2.333 | -2.6 | -4.933 | -8.746 to -1.121 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.2333 | 0.2114 | P > 0.05 | ns |
| 1 | -0.4 | 0.3624 | P > 0.05 | ns |
| 2 | -4.933 | 4.47 | P<0.001 | *** |

glucan 10-9 vs. glucan 10-12

| Treatment | glucan 10-9 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.3 | 2.633 | 1.333 | -2.479 to 5.146 |
| 1 | 5.9 | 5.167 | -0.7333 | -4.546 to 3.079 |
| 2 | 2.333 | 0.9333 | -1.4 | -5.212 to 2.412 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 0.5 | 1.333 | 1.208 | P > 0.05 | ns |
| 1 | -0.7333 | 0.6645 | P > 0.05 | ns |
| 2 | -1.4 | 1.269 | P > 0.05 | ns |

glucan 10-10 vs. glucan10-11

| Treatment | glucan 10-10 | glucan10-11 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.933 | 1.533 | -0.4 | -4.212 to 3.412 |
| 1 | 6.467 | 5.5 | -0.9667 | -4.779 to 2.846 |
| 2 | 2.667 | -2.6 | -5.267 | -9.079 to -1.454 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | -0.4 | 0.3624 | P > 0.05 | ns |
| 1 | -0.9667 | 0.8759 | P > 0.05 | ns |
| 2 | -5.267 | 4.772 | P<0.001 | *** |

glucan 10-10 vs. glucan 10-12

| Treatment | glucan 10-10 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.933 | 2.633 | 0.7 | -3.112 to 4.512 |
| 1 | 6.467 | 5.167 | -1.3 | -5.112 to 2.512 |
| 2 | 2.667 | 0.9333 | -1.733 | -5.546 to 2.079 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 0.7 | 0.6343 | P > 0.05 | ns |
| 1 | -1.3 | 1.178 | P > 0.05 | ns |
| 2 | -1.733 | 1.571 | P > 0.05 | ns |

glucan10-11 vs. glucan 10-12

| Treatment | glucan10-11 | glucan 10-12 | Difference | 95% CI of diff. |
|---|---|---|---|---|
| 0.5 | 1.533 | 2.633 | 1.1 | -2.712 to 4.912 |
| 1 | 5.5 | 5.167 | -0.3333 | -4.146 to 3.479 |
| 2 | -2.6 | 0.9333 | 3.533 | -0.2791 to 7.346 |

| Treatment | Difference | t | P value | Summary |
|---|---|---|---|---|
| 0.5 | 1.1 | 0.9967 | P > 0.05 | ns |
| 1 | -0.3333 | 0.302 | P > 0.05 | ns |
| 2 | 3.533 | 3.201 | P<0.01 | ** |