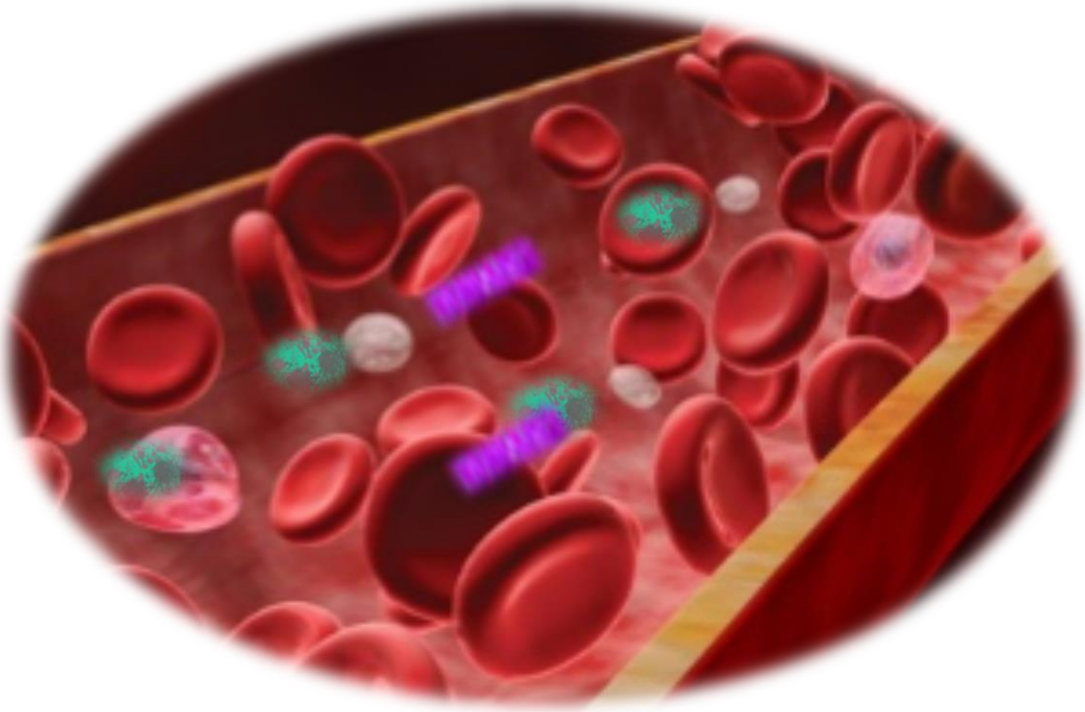
Heat Stress and Dust Pneumonia: Beta Glucans Modes of Action



THE KEY: INHIBIT IRG1 EXPRESSION

- Gram negative endotoxins induce immune cell pro-inflammatory cytokines (IL-6,IL-1, TNF) resulting in disseminated intravascular coagulation, respiratory failure, and multi-organ collapse - a systemic cytokine storm.

- When WBC's are exposed to toxin (LPS) – beta glucans inhibits the IRG1 gene of the Itaconate Pathway (fig 1) avoiding immune paralysis and activates deployment of anti-inflammatory cytokines.

- See Trained Immunity

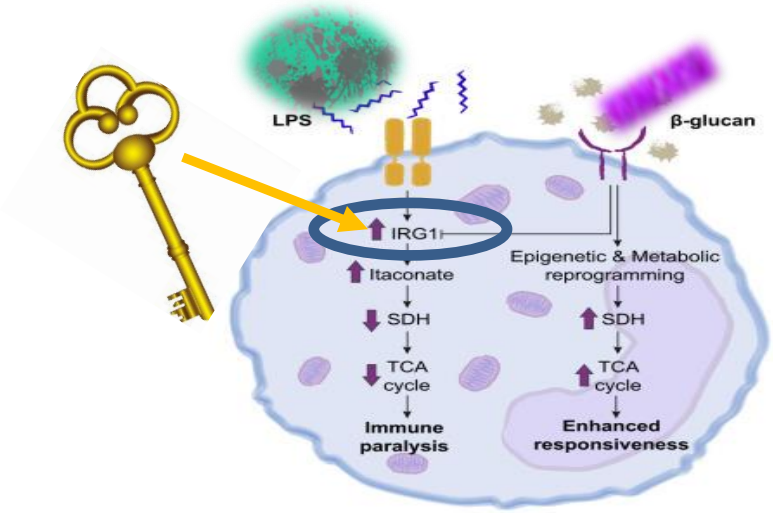
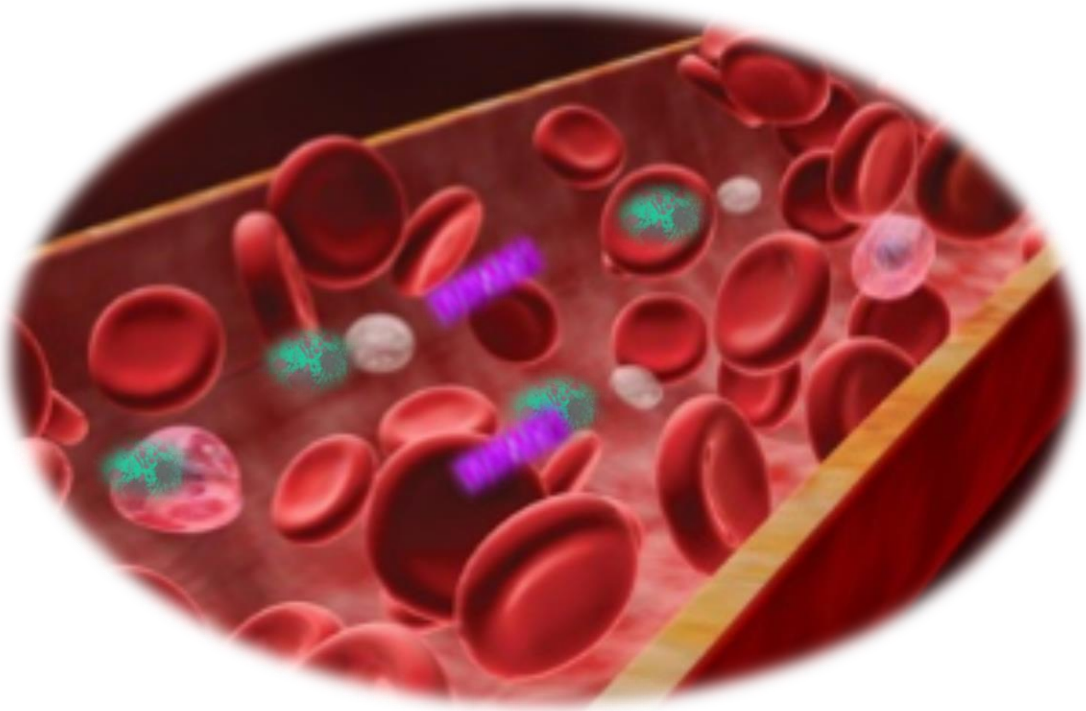


Figure 1. LPS induced itaconate pathway vs counteraction by beta-glucan
Domı´nguez-Andre´ s et al., 2019, Cell Metabolism 29, 211–220, January 8, 2019.



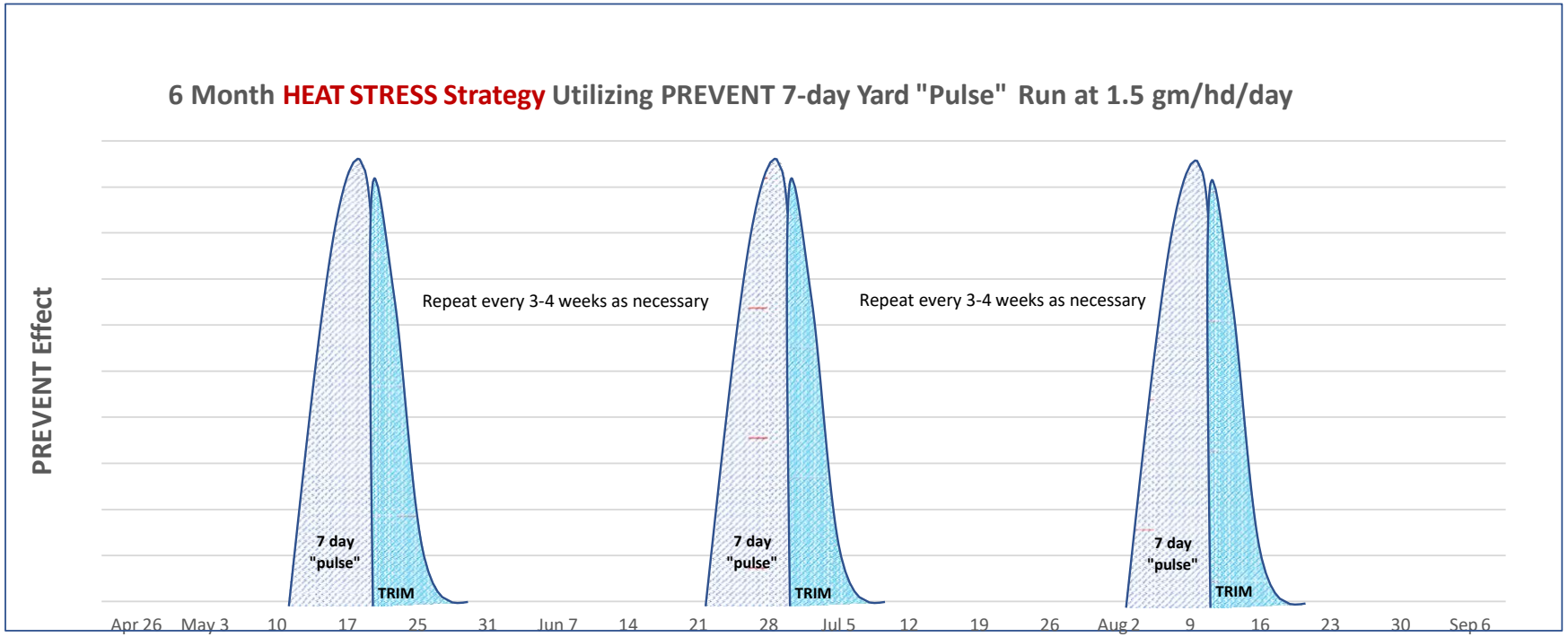
Additional Key Points: Neutrophil Activation

- It takes **2-3 days** for the lymphatic system to release fragmented beta glucans that bind to neutrophils via the CR3 and Dectin-1 receptors.

- Chemotaxis, Chemokinesis, increased expression of adhesive molecules.

- "Neutrophils move faster and sticks better to bacteria"

Start Feeding 2-3 days BEFORE the heat wave



Key Point: Trained immunity (TRIM)

Beta-glucan exerts a long term upregulation of innate immune function termed **"trained immunity" or "innate immune memory"** (Neta et al, 2019; Quintin et al, 2012).

Trained immunity, has the potential to reverse immunoparalysis associated with LPS and restores the expression of SDH in tolerant monocytes. Following exposure to beta-glucan there are a number of "reprogramming" effects within innate immune cells including:

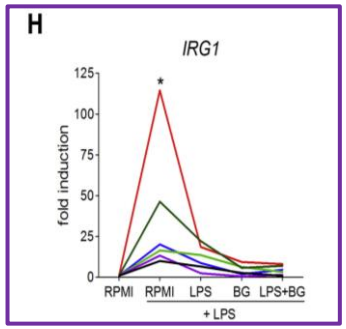
- "Memory" of training shown 7-21 days after b-glucan exposure
- Modified cellular activation
- Beneficial changes in cytokine production, i.e. decreased IL-6/TNFα
- A more robust and beneficial immune and treatment response

LPS CHALLENGE

~50-65% Inhibition of IRG1 expression

Multispecies

Vers. 7

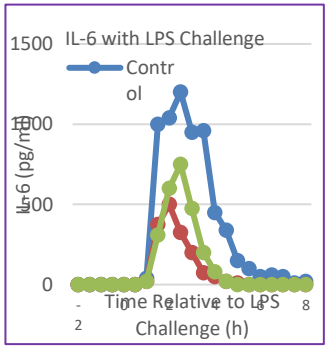


Cell Metabolism 2019 29211-220.e5DOI: (10.1016/j.cmet.2018.09.003)

LPS Challenge

~40-60% Less IL-6

Beef & Dairy Trials



Young, et al. 2012, Texas Tech

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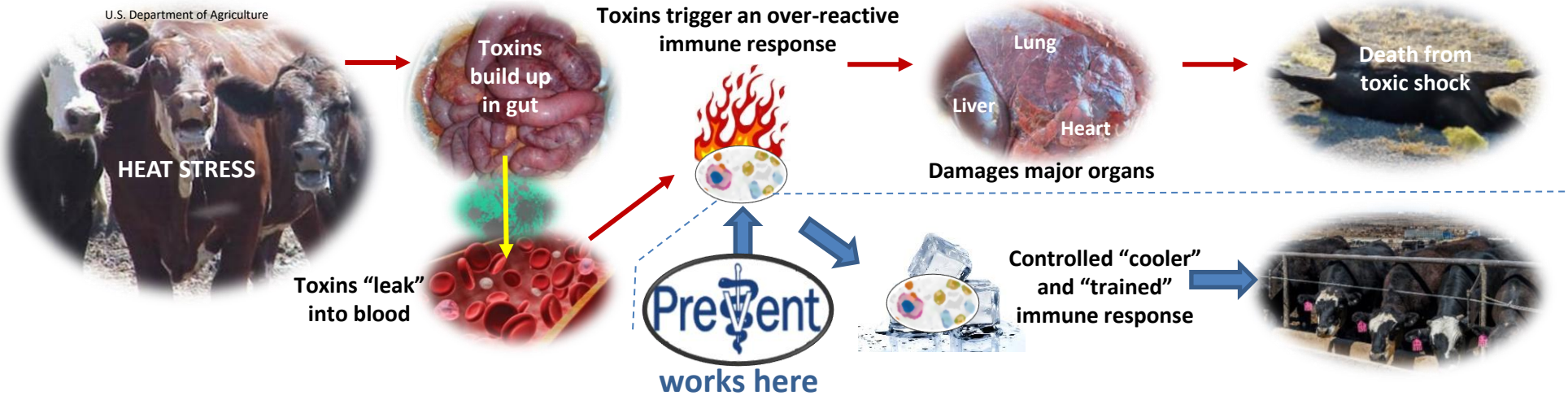


PREVENT

(Beta-glucan)

INTRODUCTION

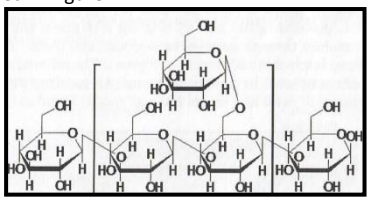
Prevent is a purified, enzymatically extracted 1-3, 1-6 beta glucan. Beta Glucans belong to a group of biologically active natural compounds called biological response modifiers. These substances represent highly conserved structural components of cell walls in yeast, fungi, grain and seaweed. As they are not found in animals, these carbohydrates are considered to be classic pathogen-associated molecular patterns (PAMPs), and are recognized by the innate immune system. [11]

MOLECULAR STRUCTURE

Glucan derived from baker's yeast (Saccharomyces cerevisiae) is a 6-branched 1,3-β-glucan which is the best characterized and has produced the highest biological effects. These polysaccharides are a heterogeneous group of glucose polymers, consisting of a backbone of β (1→3)-linked β-D- glucopyranosyl units with β (1→6)-linked side chains of varying distribution and length.

The general structure of the glucan molecule is summarized in Figure 1.

Figure 1. Beta-glucan structure



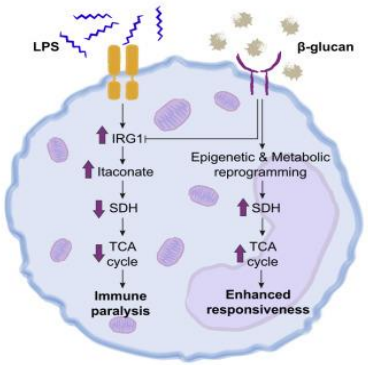
MECHANISM OF ACTION

Beta-glucan counteracts the tolerizing effects of LPS (endotoxin) by inhibiting IRG1 gene expression blocking the induction of the itaconate pathway. Itaconate is one of the most strongly upregulated metabolites in activated macrophages, accumulating in high levels after LPS stimulation (Lampropoulou et al, 2016) Figure 2.

Additionally, beta-glucan exerts a long term upregulation of innate immune function termed **"trained immunity"** (Neta et al, 2019; Quintin et al, 2012). Trained immunity has the potential to reverse immunoparalysis associated with LPS and restores the expression of SDH in tolerant monocytes. Following exposure to beta-glucan there are a number of "reprogramming" effects within innate immune cells. This includes:

- Modified cellular activation
- Beneficial changes in cytokine production, i.e. decreased IL-6 and TNFα
- A more robust beneficial immune response.

Figure 2. LPS induced itaconate pathway vs counteraction by beta-glucan.



Beta glucan binding triggers intracellular processes, characterized by the respiratory burst after phagocytosis of invading cells (formation of reactive oxygen species and free radicals), the increase of content and activity of hydrolytic enzymes, and signaling processes leading to activation of other cells and secretion of cytokines such as: interleukin 1 (IL-1) and 2 (IL-2), tumor necrosis factor α (TNF- α) and interferon α (IFN- α) [17-19].

FIELD TRIAL DATA

Receiving Trial: A total of 867 head of 665 Lb. steers and heifers split into Control and Treatment groups with 4 replicates in a SW Kansas commercial feedyard. Prevent treatment groups had statistically significant improvements in Total WBC's and Monocytes (Figure 3 and Figure 4).

Figure 3. 10% Improvement in Total WBC's, p<.01

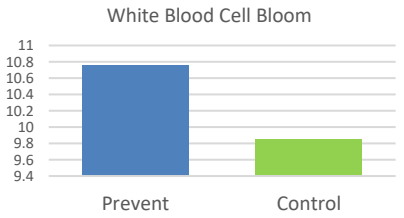
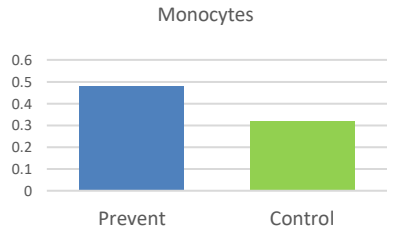


Figure 4. 41% Improvement in Monocytes, p<.001



Summary Results

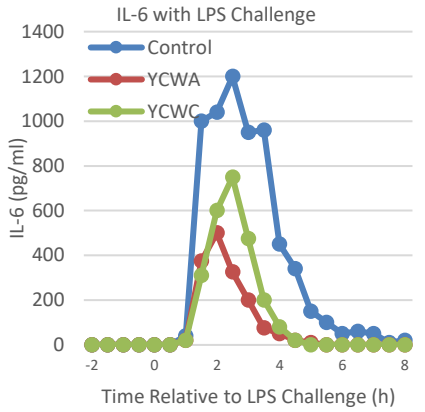
- Improved controlled immune response
- Reduced Pulls, Retreats (>50% reduction in first pulls, and >90% reduction in retreats.
- Monocytes play a crucial role in governing the initial immune response. Prevent increased monocytes by 41%.

RESEARCH

As an example, research by Young (2012, Texas Tech) on yeast cell wall (YCW) extracts demonstrated a benefit on performance and health.

Reduction in the LPS induced IL-6 cytokine is critical in reducing a heat stress induced cytokine storm (Fig. 5). YCW extracts have shown improvements in DMI and ADG with reduced morbidity consistently across multi-species heat stress and LPS challenge research experiments.

Figure 5. Cytokine storm



Heat stress results in a multitude of pathological and physiological responses. Heat stress causes significant morphological changes in the gut (Bouchama et al., 2005; Chang et al., 2013). Data to support these observations were obtained in human and animal studies. Heat exposure in livestock caused marked injury to intestine including epithelial shedding (Yu et al., 2010). These morphological changes clearly alter the integrity of the GI tract, which serves as the first line of defense against gut bacteria and endotoxins (LPS) from gram negative bacteria. Dysfunction of this barrier results in increased intestinal permeability and diffusion of toxic bacterial components from the gut lumen into the blood. This situation triggers a systemic inflammatory response that then leads to disseminated intravascular coagulation, necrosis of organ tissues, and multi-organ failure.

References

1. Domínguez-Andrés, Jorge, et al. "The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity." *Cell metabolism* 29.1 (2019): 211-220.

2. Broadway, Paul R., et al. "Some negative effects of heat stress in feedlot heifers may be mitigated via yeast probiotic supplementation." Frontiers in veterinary science 6 (2020): 515.

3. Novakovic, Boris, et al. "β-Glucan reverses the epigenetic state of LPS-induced immunological tolerance." *Cell* 167.5 (2016): 1354-1368.

4. Gillen, Joseph, et al. "LPS tolerance inhibits cellular respiration and induces global changes in the macrophage secretome." *Biomolecules* 11.2 (2021): 164.

5. Ducray, Henri Alexandre Giblot, et al. "Mitigation of heat stress-related complications by a yeast fermentate product." *Journal of Thermal Biology* 60 (2016): 26-32.

6. Koo, Sue-jie, and Nisha J. Garg. "Metabolic programming of macrophage functions and pathogens control." *Redox biology* 24 (2019): 101198.

7. Griffin, D., et al. Dust Pneumonia in Feeder Cattle, http://gpvec.unl.edu/Elective_files/feedlot/AIP_DustPneu_NG.pdf

8. Geller, Anne, and Jun Yan. "Could the induction of trained immunity by β-glucan serve as a defense against COVID-19?." *Frontiers in immunology* 11 (2020): 1782.

9. Burdick Sanchez, Nicole C., Paul R. Broadway, and Jeffery A. Carroll. "Influence of yeast products on modulating metabolism and immunity in cattle and swine." *Animals* 11.2 (2021): 371.

10. Soltys, Jindrich, and Mark T. Quinn. "Modulation of endotoxin-and enterotoxin-induced cytokine release by in vivo treatment with β-(1, 6)-branched β-(1, 3)-glucan." *Infection and immunity* 67.1 (1999): 244-252

11. Bester, Janette, and Etheresia Pretorius. "Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity." *Scientific reports* 6.1 (2016): 1-10.

12. Iba, Toshiaki, and Jerrold H. Levy. "Sepsis-induced coagulopathy and disseminated intravascular coagulation." *Anesthesiology* 132.5 (2020): 1238-1245.

13. Sandvik, A., et al. "Oral and systemic administration of β-glucan protects against lipopolysaccharide-induced shock and organ injury in rats." *Clinical & Experimental Immunology* 148.1 (2007): 168-177.

14. Liu, Jun, et al. "Curdlan (Alcaligenes faecalis)(1→ 3)-β-d-Glucan Oligosaccharides Drive M1 phenotype polarization in murine bone marrow-derived macrophages via activation of MAPKs and NF-κB pathways." *Molecules* 24.23 (2019): 4251.

15. Viola, Antonella, et al. "The metabolic signature of macrophage responses." *Frontiers in immunology* (2019): 1462.