Monophosphoryl Lipid A (MPLA) as an Innovative Immune Countermeasure to Mitigate Clinical Immunosuppression Risks for Exploration Space Missions

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OVERVIEW

- Spaceflight perturbs the human immune system. Among other manifestations, crewmembers may experience latent herpesviruses reactivation due to impaired lymphocyte function, as well as allergic/hypersensitivity reactions.
- Considering future space travel will be of longer duration (thereby increasing stress, exposure to radiation, etc…) with no rapid return option, it is of paramount importance to develop a countermeasure(s) to immune dysregulation.
- Monophosphoryl lipid A (MPLA) is a derivative of lipopolysaccharide (LPS), a potent inflammatory agent that can cause septic shock. MPLA possesses the immune-stimulatory effects of LPS without the adverse inflammatory effects.
- **HYPOTHESIS**: Treating immune cells with MPLA will boost their function enough to overcome the inhibitory effects of microgravity.

INNOVATION

While MPLA has been tested as an adjuvant extensively in mice and preliminarily for human vaccines, it has never been assessed for efficacy in microgravity.

OUTCOME

Experimental Design:

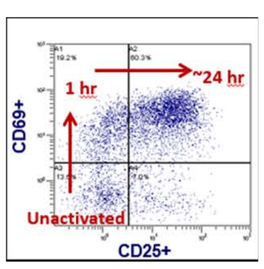
	Negative Controls:		Positive Control Stimulus:		Test Stimulus:		Test Stimulus:	
	No Stimulation		PMA + Ionomycin		SEA+SEB		anti-CD3+CD28	
PBMC	-	+	+	+	+	+	+	+
MPLA	-	-	+	-	+	-	+	-	+

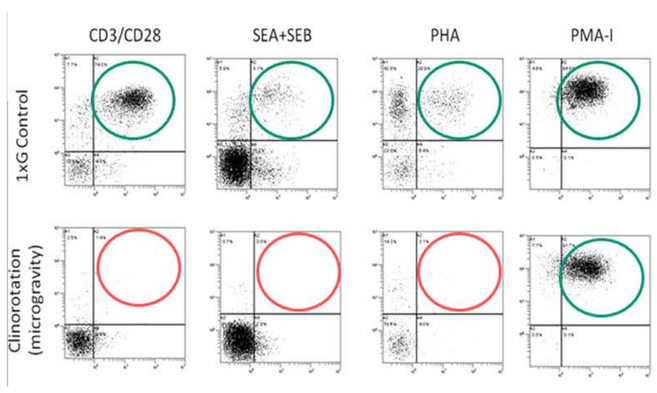
→ Static (1g) vs. Clinostat (microgravity)

→ 6-hr Cytokine Production and 24-hr Activation

- Cells receiving MPLA were treated with it for 24 hours prior to stimulation.
- Toxicity assessment: optimal concentration of MPLA for use with peripheral blood mononuclear cells (PBMC) was determined to be 5 micrograms/ml/ 1x106 cells.

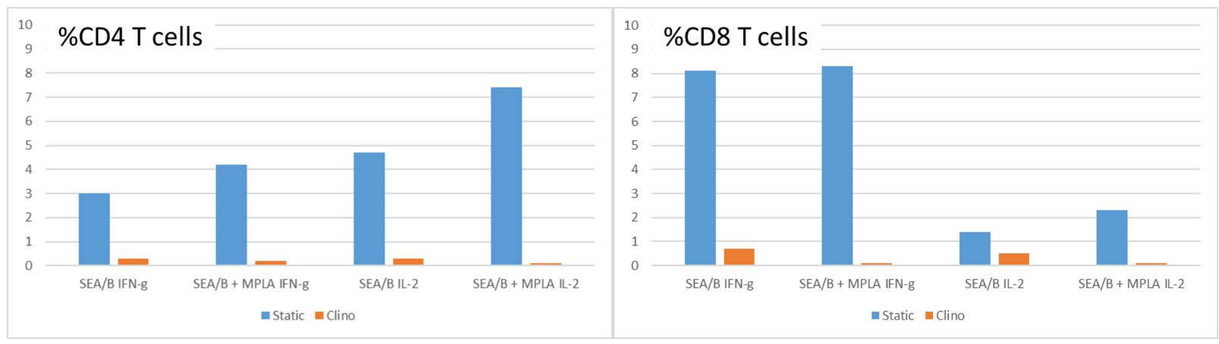
Modeled Microgravity: PBMC were stimulated with the indicated mitogens, after treatment with (or without) MPLA. Activation is measured by the expression of CD69 (Y-axis) and CD25 (X-axis). Fully activated cells progress from the lower left quadrant to the upper right quadrant. In the clinostat, T cell activation is lost (red circles). However, PMA+ Ionomycin stimulation serves as a positive control because it induces robust T cell activation even in microgravity conditions.



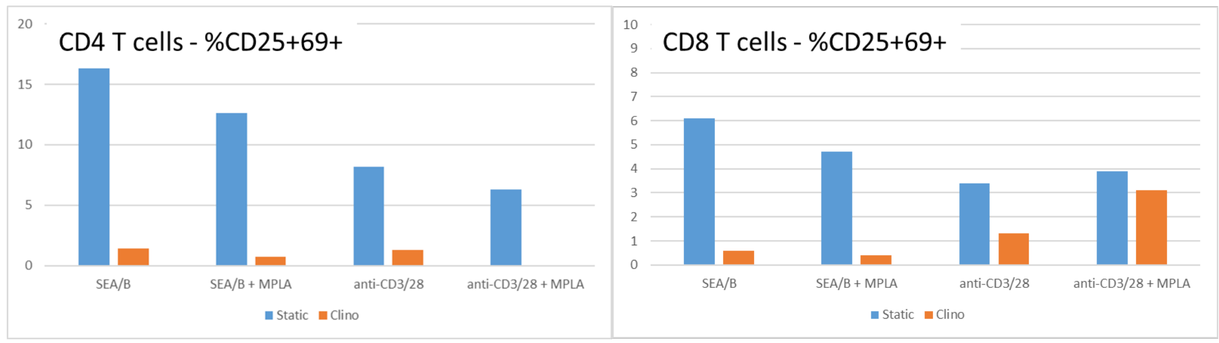


Results:

1) MPLA does not recover 6-hour cytokine production by T cells in the clinostat.



2) MPLA does not recover 24-hour activation of T cells in the clinostat.



Conclusion:

MPLA is not an effective countermeasure for T cell impairment in microgravity conditions.

INFUSION SPACE / EARTH

We leveraged our validated laboratory-based microgravity cell culture analog (the clinostat) and immune surveillance method to create an important precedent for evaluating candidate immune countermeasures robustly. Thus, this work is poised to advance the state of countermeasures research in Human Systems.

FUTURE WORK

While MPLA was not able to prevent T cell impairment, its mechanism of action suggests it will be effective at boosting the function of other immune cells; we will test its effect on monocytes and natural killer (NK) cells. Broadly, this project proves our laboratory method is optimal; we are prepared to evaluate a suite of immune dysfunction countermeasure products. Our goal is to perform similar assessments in a ground analog, such as Antarctica Winter-over, and ultimately with crewmembers aboard ISS.

PARTNERSHIPS / COLLABORATIONS

This project is a collaboration between the JSC Immunology Laboratory and Dr. Tushar Varma, Ph.D. (Imbue Pharma)