# Pegylated Arginase I Blunts T Cell Function Through Inhibition of Dendritic Cell Development

Paul Kepper, Paul Thevenot, Ph.D, Audrey Lemoine, Paulo Rodriguez, Ph.D
Stanley S. Scott Cancer Center, Louisiana State University Health Sciences Center

LSU Health NEW ORLEANS School of Medicine
Stanley S. Scott Cancer Center

Louisiana Cancer Research Consortium IN NEW ORLEANS

## Abstract

The development of an immune suppressive microenvironment plays a primary role in the growth of tumors and represents a major obstacle in the success of tumor immunotherapy. The metabolism of the non-essential amino acid L-Arginine (L-Arg) through the enzyme arginase I in myeloid derived suppressor cells (MDSCs) is a fundamental mechanism and prime example of the suppressive immune responses in tumor-bearing hosts. Accordingly, the depletion of L-Arg through a pegylated form of human recombinant arginase I (PEG-Arg I) impaired T cell function and delayed the appearance of graft vs. host disease in mice undergoing mismatched bone marrow transplantation (1). Additional results indicated that PEG-Arg I therapies induced the accumulation of MDSCs, suggesting that PEG-Arg I blocked T cell responses mainly through MDSC promotion (2). However, the specific effect of L-Arg starvation in the maturation and function of myeloid cells remains entirely unknown. In this study, we aimed to determine the effect of PEG-Arg I in the maturation of dendritic cells, the ultimate antigen-presenting cells. We hypothesize that L-Arg deprivation by PEG-Arg I hinders the maturation of dendritic cells, leading instead to the accumulation of their precursors, MDSCs. Therefore, PEG-Arg I-based therapies represent a potential therapy for conditions such as self-reactive immune pathologies or T lymphocyte reactions preceding transplantations. Our results show that the treatment with PEG-Arg I impairs T cell proliferation *in vivo* through the accumulation of MDSCs. Additional findings also indicated that PEG-Arg I blocked the development of dendritic cells *in vitro* and significantly inhibited their ability to activate T cells. These results, associated with an increased accumulation of MDSCs, suggest that PEG-Arg I blocked dendritic cell differentiation beyond an MDSC stage. Therefore, the overall results suggest that PEG-Arg I impairs T cell function through an arrest of dendritic cell differentiation. Continuation of our research is expected to have a positive public health impact as the findings could enable the development of new therapies for autoimmune disorders and increase the understanding of the important role of the metabolism of L-Arg in immunity.

## Hypothesis

**L-Arg deprivation by PEG-Arg I blocks the maturation of dendritic cells, leading to the accumulation of their precursors MDSC.**

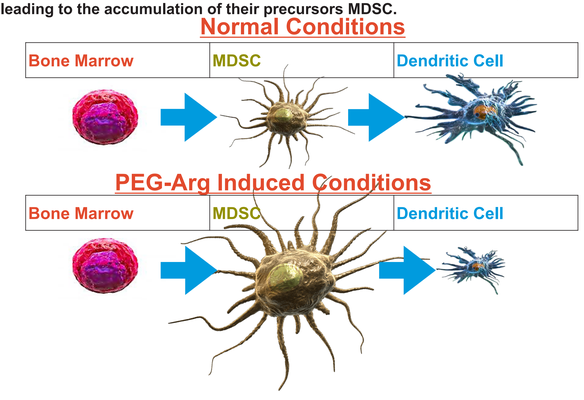
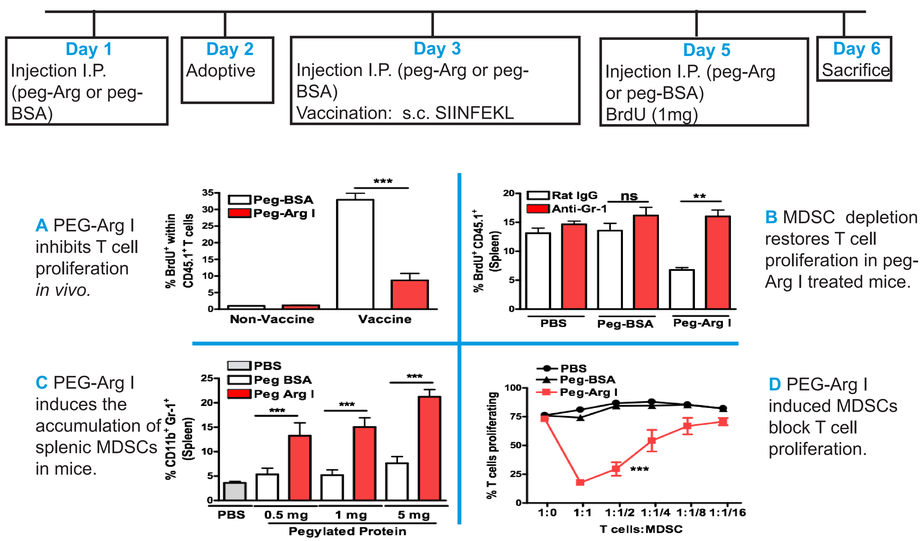



Figure 1:PEG-Arg I inhibits T cell proliferation *in vivo* through the induction of MDSCs.



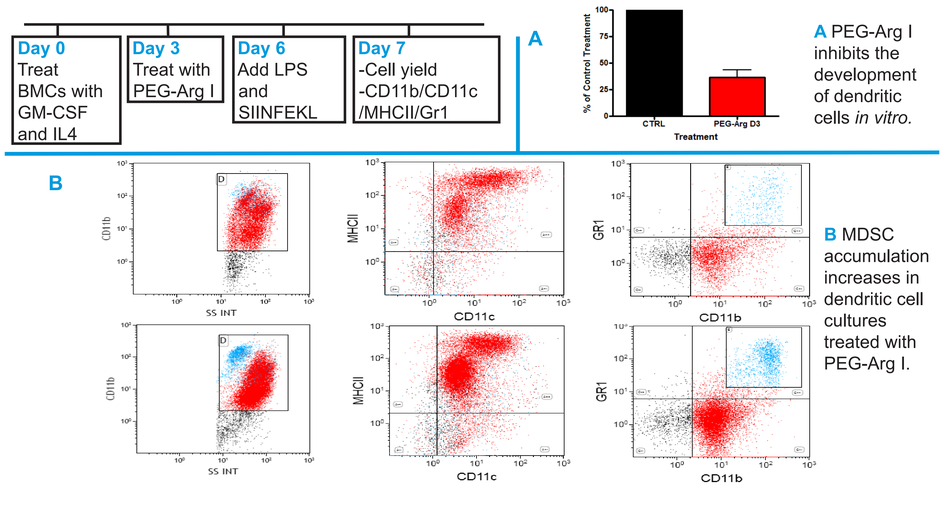

**A** PEG-Arg I inhibits T cell proliferation *in vivo.*

**B** MDSC depletion restores T cell proliferation in peg-Arg I treated mice.

**C** PEG-Arg I induces the accumulation of splenic MDSCs in mice.

**D** PEG-Arg I induced MDSCs block T cell proliferation.

Figure 2: PEG-Arg I impairs maturation of dendritic cells *in vitro* while inducing MDSCs.

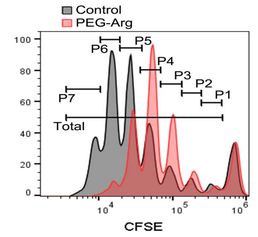



**A** PEG-Arg I inhibits the development of dendritic cells *in vitro.*

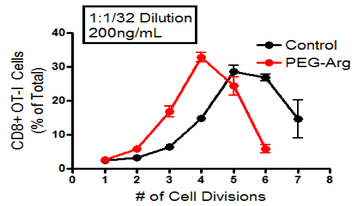
**B** MDSC accumulation increases in dendritic cell cultures treated with PEG-Arg I.

Figure 3: PEG-Arg I blocks the ability of dendritic cells to efficiently activate T cells.

**A** The development of dendritic cells in the presence of peg-Arg I blocks their ability to activate T cells.




**B** Peg Arg I treatment of dendritic cells delays the ability of dendritic cells to present antigens and activate T cells.




## Conclusions

- **PEG-Arg I inhibits T cell proliferation *in vivo* through the induction of MDSCs.**
- **PEG-Arg I impairs maturation of dendritic cells *in vitro*; resulting in greater number of MDSCs.**
- **PEG-Arg I blocks the ability of dendritic cells to efficiently activate T cells.**

Future experiments will be done to determine the role of $CD11b^{+}$ $GR1^{+}$ in the decreased function of dendritic cells developed in the presence of peg-Arg I and to characterize the pathways by which peg-Arg I prevents myeloid cell maturation. Another set of experiments will identify the effect of L-Arg deprivation in the maturation of dendritic cells *in vivo*.

## References

1. Highfill SL, Rodriguez PC, Zhou Q, Goetz CA, Veenstra R, Taylor PA, Panoskaltsis-Mortari A,Serody JS, Munn DH, Tolar J, Ochoa AC, Blazar BR. Bone Marrow Myeloid-Derived Suppressor Cells (MDSC) Inhibit Graft-Versus-Host Disease (GVHD) via an Arginase 1 Dependent Mechanism that is Upregulated by IL-13. Blood. 2010 Dec 16; 116(25):5440-1.
2. Fletcher M, Ramirez ME, Sierra RA, Raber P, Thevenot P, Alkhami AA, Sanchez-Pino MD, Hernandez CP, Wyczechowska D, Ochoa AC, Rodriguez PC. L-Arginine Depletion Blunts Anti-Tumor T Cell Responses by Inducing Myeloid-Derived Suppressor Cells. Cancer Res. 2015 Jan 15; 75(2):275-83.

## Acknowledgements

This work was partially supported by National Institutes of Health (NIH) grants P20GM103501 subproject #3 and NIH-RO1CA184185 to P.C.R.