Priscilla Do  
PhD Candidate  

“Immune attunement: fortifying anti-tumor immunity via T cell co-stimulation”  

March 29th  
James L035  
11:00AM
VITA

2010 ................................................................. BS, University of Notre Dame

2017 ................................................................. PhD, The Ohio State University

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ABSTRACT

Immune suppression is recognized as a hallmark of cancer that has gained unprecedented attention in recent years due to dramatic responses with new immune based therapies. Many therapeutic strategies are employed to reverse suppression and utilize our natural biological defense against cancerous cells. The beauty of which, is demonstrated as a non-chemotherapeutic method for long term clinical benefit and potentially, a cure. Attunement of anti-tumor immunity rests largely on provocation of adaptive immunity and the ability of T cells to remember non-self and self-dangerous signals. The naïve to effector T cell transition, accomplished through stimulation of the T cell receptor and co-stimulation through CD28, is critical for the development of this response. Presented here are two strategies in a B cell malignancy, Chronic Lymphocytic Leukemia (CLL), aimed at attunement of this T cell co-stimulatory node by influencing surrounding biological players.

The first component of this dissertation identifies Cytotoxic T Lymphocyte Antigen 4 (CTLA-4), an antagonist of CD28, as a potential therapeutic target on tumor cells. Despite clinical utility in targeting CTLA-4 on T cells, its function on non-T cells remains largely unaddressed, especially in the context of therapy. We define an immunosuppressive role for tumor expressed CTLA-4 in CLL. A majority of primary CLL samples were intracellularly CTLA-4+. Co-culture with activated T cells induced expression of CTLA-4 on the surface of CLL B cells. Expression of CTLA-4 on CLL cell lines Mec1 and OSU-CLL resulted in decreased expression of the cognate ligand, CD80, on CD80+ cells with rescue upon CTLA-4 blockade. Co-culture of CTLA-4+ Mec1 and CTLA-4+ primary CLL cells with CD80-GFP+ cells revealed transfer of CD80-GFP into primary CLL cells and Mec1 cells, consistent with the ability of CTLA-4+ T cells to trans-endocytose CD80. Additionally, co-culture of T cells with Mec1 CTLA-4+ cells resulted in decreased IL2 production, signifying reduced co-stimulation. Finally, the role of CTLA-4 on disease progression, overall survival, and anti-tumor immunity was tested in vivo using
a newly generated mouse model. We present a novel paradigm that extends the immunosuppressive role for CTLA-4 beyond expression on T cells.

The second component of this dissertation investigates a novel immunomodulatory drug, CC-122. Structurally, CC-122 is closely related to Lenalidomide (Lena), a pleiotropic immune modulator approved for multiple myeloma, myelodysplastic syndrome, and mantle cell lymphoma that activates B, T, and NK cells. Unique to CLL therapy with Lena is a potentially fatal, dose-limiting toxicity known as tumor flare. Because Lena is hypothesized to work through restoration of T cell function, including promotion of co-stimulation, CC-122 and Lena were compared in this context. A key difference was discovered between CC-122 and Lena treated activated CLL T cells by gene expression analysis. CXCL13, a B cell chemoattractant, was ≥3 fold increased with Lena v. CC-122. Overexpression of the CXCL13 receptor, CXCR5, in CLL but not MM may contribute to migration of CLL cells to the lymph nodes and potentially tumor flare. Retaining the anti-tumor activity of Lena while mitigating tumor flare is of clinical interest and critical to the development of CC-122.

Overall, these studies reveal basic biological mechanisms in cancer immunology that are applicable to CLL and potentially other diverse malignancies.
RECENT ABSTRACTS AND PRESENTATION


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AWARDS AND HONORS

2017 American Association of Immunologists Trainee Abstract Award
2016 American Society of Hematology Abstract Achievement Award
2014 Pelotonia Graduate Student Fellowship

FUTURE PLANS

I will be pursuing a post-doctoral fellowship and continuing in academia.
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