



## 2007 Research Grant Program Winning Abstract

### The Role of Plasmacytoid Dendritic Cells

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Although tumors express tumor-associated antigens (TAA), the spontaneous clearance of established tumors by the immune system is rare. Many studies have shown that tumors employ numerous strategies either to prevent presentation of TAA, or to prevent TAA presentation in the context of T cell costimulatory molecules. Thus, it was thought that lack of TAA-specific immunity was largely a passive process where tumors simply did not present enough TAA, or antigen-presenting cells did not have sufficient stimulatory capacity. However, recent work demonstrates that this is not the case. Lack of naturally induced TAA-specific immunity is not simply a passive process whereby adaptive immunity is shielded from detecting TAA. In fact, data from our lab and others demonstrate that tumors actively prevent induction of TAA-specific immunity through induction of TAA-specific tolerance.

Human plasmacytoid dendritic cells (PDCs) arise from cells lacking lineage markers and CD11c, but expressing HLA-DR. PDCs are further identified phenotypically by expression of CD123, the IL-3R $\alpha$  chain. PDCs can activate natural killer (NK) cells and induce a Th1 immune response in T cells through the production of type I interferons. PDCs have also been shown to mediate antigen-specific immune tolerance. Furthermore, PDCs have been reported to induce CD4+CD25+ regulatory T cell (Treg) differentiation.

Tregs are a group of lymphocytes that serve the dual roles of preventing autoimmune disease and regulating pathologic immune responses. CD4+CD25+ Tregs are elevated in human cancers. Our lab recently showed that they inhibit TAA-specific immunity and predict poor survival in human ovarian cancer. Furthermore, the malignant ascites of ovarian cancer harbors numerous functional CD4+CD25+ Tregs. Little regarding PDC-mediated immunity in cancer is known. However, we recently demonstrated a role for PDC in immunopathogenesis of ovarian cancer, including induction of Tregs. We hypothesize that tumor PDC-induced Tregs inhibit TAA-specific immunity and facilitate tumor growth, thus contributing to cancer immunopathogenesis. Therefore, understanding these processes is central to unraveling the immunopathologic basis of cancer.

To investigate these processes, a flow cytometry-based approach using a BD LSR II and a BD FACSAria will be employed. We will also utilize a BD Pathway 855 bioimager for the development of novel assays and approaches to study cancer immunopathogenesis. Importantly, we will use BD Biosciences technologies and reagents to pursue two testable hypotheses as specific aims for this project. Insights gained from this work will translate into novel strategies to overcome immune dysfunction in tumors, and reversal of this dysfunction may allow successful immunotherapy.



Our specific aims:

**Aim 1:**

Test the hypothesis that T cells activated by tumor PDC block TAA-specific immunity. Tregs in ascites or tumor can block effector T cells whereas Tregs in LN can inhibit naïve T cell priming. We will use BD Biosciences reagents along with in vitro models for human immunity to test Treg effects on naïve T cell priming and on defined TAA-specific effector cell functions including cytokine secretion, proliferation, and cytolytic activity. Further studies will test whether PDC-activated Tregs exhibit the contact-dependent mechanistic features of classic CD4<sup>+</sup>CD25<sup>+</sup> Tregs (working through CTLA-4) or features of Tr1-like Tregs which inhibit immunity through soluble mediators such as IL-10.

**Aim 2:**

Test the hypothesis that T cells activated by PDCs block immune-mediated tumor rejection in vivo. There are several novel chimeric SCID/NOD mouse models in which we can adoptively transfer human ovarian carcinoma tumors plus autologous immune effector and Treg cells. This model allows for testing of Treg function, TAA-specific immune suppression and tumor growth in vivo in an autologous setting. We will use this model to test whether tumor PDC-activated T cells can inhibit TAA-specific immunity in vivo and block immunologic tumor rejection. Mechanisms will be tested by blocking IL-10, CTLA-4 or other Treg effector mechanisms in vivo.

These studies will allow us to study the role of PDCs and Tregs in tumor immunity and tolerance. In order for active tumor immunity to be engendered, either naturally or experimentally, the tolerizing conditions of the tumor microenvironment must first be overcome. Means to revert these tolerizing conditions represent a novel therapeutic strategy against ovarian cancer and other malignancies.

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