

# Presenting: Antigenes, Dendritic Cells, and IDO

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Hippocrates once said, “As to diseases, make a habit of two things — to help, or at least, to do no harm.” Although relevant to everything we do in medicine, the field of hematopoietic stem cell transplant (HSCT), tarnished by graft-versus-host disease (GVHD), is certainly befitting of such wisdom. The quest to harness the desired anti-tumor effects of HSCT while limiting GVHD is ongoing, and has added much to our understanding of the anti-tumor mechanisms of HSCT. In spite of our success in employing HSCT in the setting of numerous hematologic malignancies, we do not yet fully understand the mechanisms that lead to the desired graft-versus-leukemia (GVL) effects and the dreaded GVHD, the latter occurring in up to 50 percent of patients receiving allogeneic grafts despite adequate immunosuppressive prophylaxis. The immune effects of HSCT are dependent on a complex interaction between antigens, cells, and signaling molecules. How does antigen presentation affect GVL and GVHD? How do dendritic cells (DC) regulate these outcomes? What molecules regulate tolerance versus immunity?

During the Scientific Committee on Transplantation Biology Session, which will be held today from 2:00 – 3:30 p.m. and 4:00 – 5:30 p.m., Dr. Warren Shlomchik will discuss antigen presentation in GVHD and GVL. Although most investigators have focused on T cells as mediators of the immune effects of HSCT, antigen-presenting cells (APC) share an equally important role in initiating and maintaining GVHD and GVL. Recipient- and donor-derived APCs have distinct functions in acute and chronic GVHD, which determine the extent of the immune response and the target tissues involved. Selectively targeting APC subpopulations in HSCT may therefore provide a mechanism by which the deleterious consequences of GVHD can be minimized while exploiting the full potential of GVL effects.

Dr. Shlomchik will be followed by Dr. Edgar Engleman, who will address the role of DC-based tumor immunotherapy. DCs are the most potent APCs as they have the capacity to present new antigens, provide costimulatory signaling, and activate both innate and adaptive immune responses. Although most DC-based vaccine studies have concentrated on *in vitro* manipulation of DCs prior to administration to tumor-bearing host and have yielded promising results, they have failed to translate into significant clinical responses. The focus has therefore shifted to enhancing DC functions *in vivo*. Unfortunately, DCs present in the tumor milieu are immature and more likely to promote an immunosuppressive response, and in addition are hindered by cytokines secreted from tumors such as IL-10 and TGF- $\beta$ . Nevertheless, models employing agents that either activate DCs *in vivo* or alter the tumor microenvironment appear promising and may change the future of DC-based immunotherapy.

Finally, Dr. David Munn will discuss the role of indoleamine 2,3-dioxygenase (IDO) in immune regulation. IDO is an intracellular tryptophan degrading enzyme found in specific DC subsets. It is induced by a CTLA4<sup>+</sup> subpopulation of CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells as well as interferon (IFN)- $\gamma$ , implying an important role for IDO in putting a brake on immune activation. IDO may induce T-cell tolerance to antigenic stimuli by numerous proposed mechanisms, including the depletion of the essential amino acid tryptophan, thereby causing T cells to undergo cell-cycle arrest, producing toxic metabolites leading to T cell apoptosis, or by altering the function of IDO-expressing APCs leading to immune suppression.