

## **Title: The Role of KIR and HLA in Kidney Transplantation**

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### **Synopsis:**

Although Natural Killer (NK) cell alloreactivity has been shown to correlate with improved survival after hematopoietic cell transplantation (HCT), the contribution of NK to the success or failure of organ transplants has been less well examined. NK cells act to regulate both innate and adaptive immunity. The multifunctional NK cells act as cytotoxic effectors and/or cytokine producers and regulators, engaging with a wide range of immunologic effector cells to control the immune response. NK cells can respond to (e.g. IL-2, IL-12, IL-15) or secrete (e.g. INF-gamma, TNF) an array of cytokines in the inflammatory response. NK activity is controlled by several families of cell surface receptors including the Killer immunoglobulin-like receptors (KIR), which use HLA class I as their cognate ligands. Experimental evidence in mouse models hint at a role for NK cells in organ allograft rejection, wherein NK cell depleted CD28<sup>-/-</sup> mice tolerate both haploidentical and fully mismatched cardiac transplants, interpreted as evidence that without NK cells to recognize missing-self, an allograft can be tolerated. In humans too, there are suggestions of a role for NK in organ allograft rejection, including a correlation between missing KIR ligands in recipients and the presence of alloreactive NK cells and transplant rejection.

KIR are polygenic, with between 6-14 genes per haplotype. Like HLA, KIR are highly polymorphic, with both gene families demonstrating the tell-tale footprint of rapid evolution. Because of the high level of heterogeneity in these gene clusters, large cohorts are needed to unravel the significance of association. No studies to date have rigorously analyzed both KIR and HLA genetics in kidney transplantation outcome using an adequately sized cohort. The most rigorous studies to date include an analysis of only HLA-ligands with outcome in a large kidney transplant cohort, and two studies of HLA/KIR in kidney transplant in very small cohorts; no association was found with HLA ligand status alone, and an increase in inhibitory KIR/HLA status in recipients provided less rejection in those patients.

In our proposed project, we will analyze the KIR and HLA genes and clinical data from a large, well characterized cohort of 650 donor-recipient kidney transplant pairs in collaboration with the Salomon (Scripps, CA) and Heeger (CTOT-1; Mt. Sinai NYC) laboratories to investigate the role these gene complexes play together in kidney transplant outcome.