and Aurora Kinase A Pathways ($P < .01$). Both of these represent targetable pathways with clinically-available novel therapeutics.

Sirolimus resulted in partial downregulation of proliferation and cytotoxicity pathways. However, many genes and networks were shared between the Sirolimus and GvHD cohorts, indicating inadequately controlled activation. These prominently included upregulation of the FOXM1 and IRF8 transcription factors, involved in cell cycle progression and interferon signaling ($P < .01$), respectively. Both GvHD and Sirolimus also demonstrated upregulation of the CD28, CCR5, IL-12 and IL-17 pathways ($P < .05$), all targetable with FDA-approved therapeutics (CTLA4-Ig, maraviroc, ustekinumab).

Conclusions: This is the first description of the primate GvHD transcriptome. This network approach has identified previously unappreciated genes and pathways associated with GvHD, for which several novel therapeutic strategies are immediately available for pre-clinical and clinical evaluation.

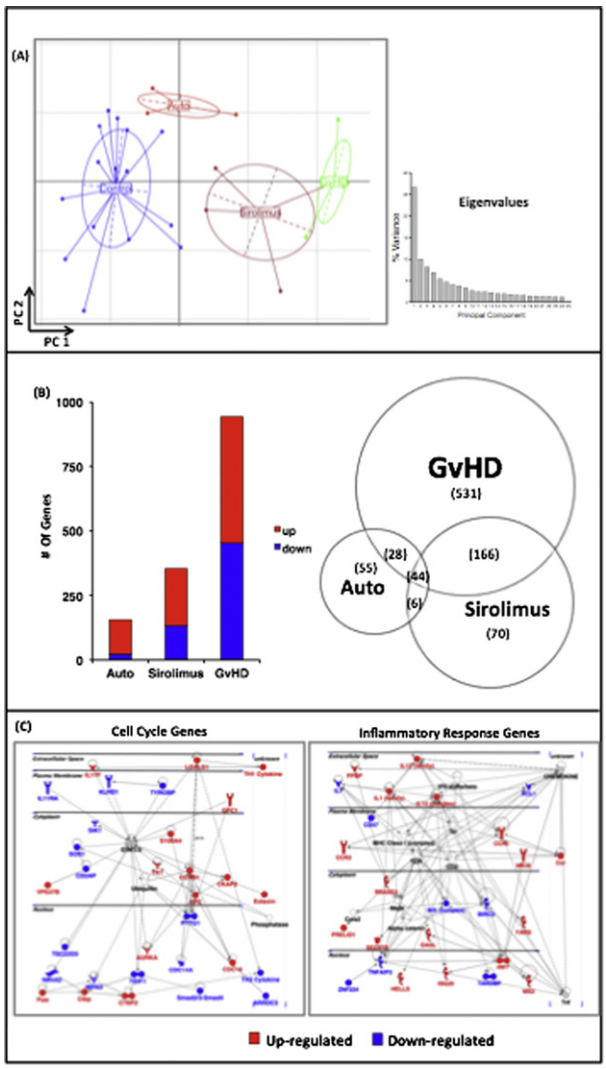

Figure 1. The Primate GvHD Transcriptome: (A) Principal Component Analysis (PCA) reveals that maximal variation between the arrays was determined by the experimental cohort. (B) Differentially Expressed (DE) Genes Compared to Healthy Controls (HC). Left: Shown Are numbers of Up- (red) and Down- (blue) regulated genes in Auto, Sirolimus, and GvHD cohorts compared to HC. Right: Venn Diagrams showing overlap of DE genes between the three cohorts. (C) Ingenuity Pathway Analysis depicting gene networks differentially regulated during GvHD. Shown are representative networks showing cell cycle (left) and inflammatory response genes (right).

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Th$_{17}$-Related Gene RORγt Overexpressed in Patients with Chronic GVHD: New Insights for T-Cell Manipulation and GVHD Control

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Introduction: Graft-versus-host disease (GVHD) is on of the leading complication of allogeneic hematopoietic stem cell transplantation (HSCT) causing significant morbidity and mortality. CD4+ T-cells play a critical role in mediating GVHD, and much effort has been devoted to studying the effect of CD4+ T-cells during the pathophysiology process of GVHD. Even though just accounting for 5% of the total CD4$^+$ T-cell population, the most promising candidates are naturally occurring CD4+CD25+ regulatory T cells (T_{regs}), which are on of the regulators of immune responses. TH$_{17}$ is a newly identified T-cell lineage that secretes IL-17, a proinflammatory cytokine. However, the functional role of TH$_{17}$ cells in the development of GVHD has not been well characterized in humans. The aim of our study was to characterize the expression of T_{reg} (*FOXP3*) and TH$_{17}$-related (*RORγt*) genes in peripheral blood of patients undergoing HSCT and correlate them with the development of GVHD in HLA identical allogeneic HSCT.

Patients and Methods: Samples were collected from peripheral blood of 50 patients before and after HSCT and at the time of GVHD onset. Thirty patients were diagnosed as acute leukemia/myelodysplastic syndrome, eleven as chronic myeloid leukemia and ten with lymphomas. Seven healthy donors were used as controls. All patients received HLA-identical related donor graft. Except for lymphomas patients (n=10), who underwent non-myeloablative conditioning, others underwent myeloablative conditioning regimens (n=40). Expression of *FOXP3* and *RORγt* were assessed by Real-Time quantitative PCR (qPCR) using the 7500 Fast Real Time PCR System (Applied Biosystems), by Taqman method. Comparison among groups was performed using Graphpad Prism 5 and Mann-Withney test.

Results: Median age for the 50 analyzed patients was 36 years-old (range: 17-60), 52% were female. 50% had GVHD, with an average onset of 39 days after HSCT for acute GVHD (range: 12-93) and 182 days for chronic GVHD (range: 117-266). No significant association was observed between *FOXP3* expression and patients with or without GVHD. On the other hand, *RORγt* showed significantly higher expression in patients with chronic GVHD compared to samples before HSCT ($P < .0001$), without GVHD ($P < .0001$) and acute GVHD ($P = .0006$). Both *FOXP3* and *RORγt* showed significant statistical decreased expression in patients compared to healthy controls, except for *RORγt* expression in patients with chronic GVHD (p=NS).

Conclusion: *RORγt* showed significantly higher expression in patients with chronic GVHD compared to samples before HSCT, without GVHD and acute GVHD. These findings suggest a Th17/IL-17 mediated proinflammatory state involved in chronic GVHD, showing a potential target for GVHD control.

Disclosures: No relevant conflicts of interest to declare.