A Phase II Exploratory Study To Evaluate the Safety of Induction Therapy with Campath-1H®, Combined with Chronic Immunosuppression with MMF and Sirolimus: A Study of the Cooperative Clinical Trials in Pediatric Transplantation.

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Background: Pediatric renal transplant recipients have excellent short-term outcomes but long-term success is compromised by complications of chronic immunosuppressive medications and chronic allograft nephropathy. Studies show that calcineurin inhibitors and steroids can be individually avoided in pediatric renal transplantation. Building on that experience we designed this study to optimize short and long-term renal allograft function with minimal chronic immunosuppression using a steroid-free, calcineurin inhibitor withdrawal protocol in low risk pediatric renal transplant recipients.

Methods: Unsensitized pediatric recipients of a first living donor kidney transplant received 2 doses of Campath-1H® (0.3 mg/kg), 1 day pre- and post-transplant. Subjects received tacrolimus and MMF immediately post-transplant until week 8-12 when they underwent protocol renal biopsy and were changed to sirolimus and MMF if rejection free. The planned 35 subjects have been enrolled; this report describes the clinical outcomes of the 23 with 1 year of follow up.

Results: The mean subject age is 12.9 yrs; 59.3% are female and 70.4% Caucasian. At transplant, 16/23 were CMV seronegative and 16/23 were EBV seronegative. Protocol therapy was discontinued in eight subjects due to: rejection (3), mouth ulcers (2), leukopenia (1), unrelated (2). Clinical acute rejection (AR) occurred in 4 subjects (17%) and 2 had subclinical AR; AR was cellular rejection in 5 subjects, and humoral in 1 at 4 days post-transplant who had an undetected positive crossmatch to Class II HLA. There were two graft losses, one due to recurrent FSGS and one due to medication non-adherence. There were no cases of PTLD and no deaths. Leukopenia occurred in 11 subjects (47.8%). There were 9 infections of which 7 were urinary tract infections (34.7%) and 2 were pneumonia (8.7%).

Conclusions: Minimization of immunosuppression using a steroid-free, calcineurin withdrawal protocol in low risk pediatric renal transplant recipients appears to be well tolerated with acceptable rates of clinical AR and no serious infections 12 months after transplantation.

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Prediction of Acute Renal Allograft Rejection by Gene Expression in
Blood, Urine and Graft Biopsies. Terry B. Strom,1 Manikkam Suthanthiran,2 David Ikle,3 P. Putheti,1 R. Ding,2 Nancy D. Bridges,4 Mohamed H. Sayegh,1 William E. Harmon.1 *1Harvard Medical School, Boston, MA; 2Weill Medical College of Cornell University, New York, NY; 3PPD Corporation, Wilmington, NC; 4Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Disease, Bethesda, MD.*

33 pediatric subjects were entered into a prospective pilot trial of calcineurininhibitor avoidance, sponsored by NIAID's Cooperative Clinical Trials in Pediatric Transplantation. Eleven subjects experienced first acute rejection episodes. Blood and urine were collected at 10 assigned times throughout the study and surveillance protocol biopsies were obtained at 0, 3, 6 and 12 months post-transplant. Samples were also obtained at times of suspected rejection. Using a sensitive target sequence-specific preamplification
strategy, quantitative expression of the Granzyme B, IP10, FOXP3, IL-15 and TGFβ1 genes was analyzed via PCR from 181 blood, 234 urine and 117 biopsy samples. Results were log-transformed and univariate and multivariate distributions were explored. Repeated assay data on individual subjects were summarized using means, deltas from first specimen to final or first rejection, and slopes of linear regression lines by time on study, and were compared between those with acute rejection and all others. Results: In urine, levels of IP10 and FOXP3 mRNAs are different and the slopes of Granzyme B and IP10 ($p<0.04$) are significantly more positive in those with rejection. In biopsies, slopes in Granzyme B ($P<0,01$) and IP10 ($p=0.08$) are more positive in rejecters and deltas of Granzyme B are different ($p=0.01$) between groups. In blood, the means of Granzyme B ($p<0.04$) are different and the slopes in FOXP3, Granzyme B, IL-15, IP10 and TGFβ1 are all significantly more positive ($p<0.01$) in rejectors. Using logistic regression to predict acute rejection from the subject-specific slope of the expression of each gene over time, all 5 are correlated with each other and all together correctly identify 10 of the 11 subjects with acute rejection. Thus analysis of recipient blood and urine for expression of informative genes may predict acute rejection of kidney transplants. Blood samples may provide the most informative results. As the molecular signature of rejection antedates deterioration in renal function tests, a practical means of identifying patients with adverse anti-donor immunity (rejection) before clinically detected renal injury may be at hand.