Novel Urinary Biomarkers of Interstitial Fibrosis/Tubular Atrophy Progression in Kidney Transplantation

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THESIS

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LIST OF ABBREVIATIONS

ABCAN   Angiotensin II Blockade in Chronic Allograft Nephropathy

BMI   Body Mass Index

CKD   Chronic Kidney Disease

DGF   Delayed Graft Function

eGFR   Estimated Glomerular Filtration Rate

FDR   False Discovery Rate

GFR   Glomerular Filtration Rate

IF/TA   Interstitial Fibrosis/Tubular Atrophy

NGAL   Neutrophil Gelatinase-Associated Lipocalin

SUMMARY

Interstitial Fibrosis/Tubular Atrophy (IF/TA) is a common problem in kidney transplantation that ultimately leads to allograft failure. There are no early non-invasive biomarkers of IF/TA available that can be used to identify early IF/TA where interventions can be implemented to prevent irreversible injury. The object of this work is to identify novel biomarkers of IF/TA in the urine of kidney transplant recipients using proteomic methods.

Mass spectrometry with isobaric tagging with iTRAQ labeling was used to quantify protein abundance in urine samples. We used individuals from two separate cohorts to identify these biomarkers. The discovery phase of the study used a cross-sectional cohort to identify candidate biomarkers of IF/TA. The validation phase used the prospective cohort to see which of the candidate biomarkers could predict progression of IF/TA.

From a sample size of 24 in the cross-sectional cohort, we identified 55 candidate biomarkers that were upregulated in at least of the 1 of the fibrosis comparisons (none-mild, none-moderate/severe, mild-moderate/severe). In the validation cohort, 4 of these biomarkers were able to differentiate progressors versus non-progressors of IF/TA. These biomarkers include alpha-1-acid glycoprotein, alpha-2-macroglobulin, apolipoprotein A-IV, apolipoprotein C-III, immunoglobulin J chain, pigment epithelium-derived factor, profilin-1, and retinol binding protein 4.

SUMMARY (continued)

Using proteomic methods, we identified 4 novel urinary biomarkers of IF/TA in kidney transplant recipients. Further studies are needed to confirm these findings and assess the clinical utility of these biomarkers in transplantation.

I. INTRODUCTION

Kidney transplantation is the preferred method of renal replacement therapy in those with end-stage renal disease. While transplantation has become increasingly routine, long-term outcomes have not improved much. Graft loss from interstitial fibrosis and tubular atrophy (IF/TA) and its major subset, IF/TA-NOS (no evidence of specific etiology), is widely acknowledged as a major problem that has increased in prominence as the incidence of acute rejection has declined. Studies from various centers suggest that, excluding patients dying with a functioning graft, as many as 80% of patients who return to dialysis do so because of IF/TA-NOS (1-4). The clinical manifestations of IF/TA-NOS conform to those of many chronic progressive renal diseases, i.e. proteinuria, hypertension and declining glomerular filtration rate (GFR) (5). Most important, much of the renal injury occurs in silence. Once the clinical manifestations such as GFR decline develops, injury is typically far advanced and the fall in GFR inexorably progresses to frank renal failure over an average of 3-4 years (6-9).

The natural history of IF/TA was best elucidated by Nankivell et al (8). In their studies of kidney/pancreas transplant recipients who underwent serial kidney biopsies, they described two stages of fibrosis. The first stage occurs within the first year of transplant and exhibits tubulointerstitial damage that is mainly ischemic in nature. These changes were more commonly seen in recipients that had either acute tubular necrosis, severe acute rejection or subclinical rejection. The second stage, occurring after the first year, shows progressive microvascular

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and glomerular damage. The most commonly associated risk factor for these latter changes was calcineurin-inhibitor toxicity. The most striking feature of this analysis was the almost universal presence of IF/TA; announcing it as the most important problem facing the transplant community today.

To prevent irreversible damage to the allograft, early predictors of its development are needed but are greatly lacking. Currently, the only method available for early diagnosis is protocol biopsies of the kidney. This approach is invasive and, most importantly, institutions who do this routinely do not have superior results to those who do not suggesting that even surveillance might be insufficient (10). Proteomic methods applied to urine, conversely, are non-invasive and have revealed biomarkers that coincide with allograft dysfunction including acute rejection. These techniques may, therefore, provide non-invasive means to detect early biomarkers for IF/TA that can be used to predict this serious entity that lacks any therapeutic options.

Proteomics is emerging as a promising tool in the study of kidney disease. For example, Stone et al. applied a serum proteomic approach to assess the state of remission in Wegener's granulomatosis (11). Utilizing 82 samples (42 in remission and 40 with active disease) their proteomic approach was able to categorize 35 out of 37 remission samples correctly with a sensitivity of 95% and 32 out of 35 active disease samples correctly with a specificity of 91%. Mischak et al, examined urine samples from 39 healthy individuals and from 112 patients with type 2 diabetes with different degrees of albuminuria(12). After establishing a normal polypeptide pattern in the urine of healthy subjects, these investigators

were able to document the presence of a specific diabetic pattern of polypeptide excretion. This peptide pattern was seen in patients with high-grade albuminuria and in 35% of those who had low-grade albuminuria and in 4% of patients with normal albumin excretion. Proteomics is also being applied to study kidney health and disease in renal transplant recipients. Biochemical markers have been sought in acute allograft rejection using various proteomic techniques. Two separate groups have found β2-microglobulin as a potential urinary biomarker for acute cellular allograft rejection (13, 14). Other techniques have yielded other biomarkers or profiles in the diagnosis of acute allograft rejection (12, 15, 16). However, very few studies have reported uniform biomarkers in IF/TA. Recently, Quintana et al. analyzed urine from kidney transplant recipients with IF/TA or chronic active antibody-mediated rejection and found distinct urinary proteomic profiles in these two groups that were different from patterns observed in controls (17). Therefore, it is plausible that certain urinary biomarkers will differentiate IF/TA that is not explained by drug toxicity or hypertension-related changes compared to those without IF/TA.

II.   METHODS

All urine samples were collected after informed consent and the protocols were approved by the institutional review boards at the University of Minnesota Medical Center and Hennepin County Medical Center.

A.   Cross-Sectional Cohort

In this cohort, urine samples were obtained from kidney transplant recipients who returned to the transplant clinic or were hospitalized at the University of Minnesota for clinical graft deterioration. As per protocol, all individuals that consented for the study had urine specimens stored at -80C for future analysis. A subset of this cohort underwent a kidney transplant biopsy at the discretion of their treating physician. For the purposes of this study, only those that had a urine specimen and a kidney biopsy were included. Further inclusion criteria were those without diabetes and biopsies that show only chronic changes with no evidence of acute cellular or vascular rejection, BK nephropathy, pyelonephritis, or C4d positivity suggesting chronic antibody mediated rejection. Additional clinical data collected at the time of the biopsy included demographics, post-transplant immunosuppression, delayed graft function, estimated GFR (eGFR), and biopsy findings.

B.   Prospective Cohort

Urine samples for the prospective cohort were collected as part of the Angiotensin II Blockade in Chronic Allograft Nephropathy (ABCAN) study (18).

Briefly, this study enrolled 153 kidney or kidney/pancreas transplant recipients in a randomized, double-blind placebo-controlled primary prevention trial which aimed to determine if, given similar blood pressure control in the two study groups, angiotensin II receptor blockade can prevent or decrease IF/TA in the allograft as measured by cortical interstitial volume expansion and GFR decline over the 5-year duration of the trial. This study performed protocol biopsies at study entry and at study exit 5 years later. Early morning voided urine samples were collected annually and stored at -80C for future studies. Upon entry of the study and during annual visits, the subjects had their GFR, urine protein, urine albumin/creatinine, and serum creatinine measured.

C.   Urine Sample Preparation and iTRAQ Labeling

Urine samples were concentrated from 1.5-2mL to approximately 50-150uL using Amicon Ultra-15 3kDa centrifugal filter units (Millipore Corp, Billerica, Ma). The concentrated solution was then transferred to Slide-A-Lyzer 3.5kDa Mini Dialysis Units (Thermo Scientific, Rockford, IL) and dialyzed against 50mM ammonium bicarbonate (pH 7.8) for at least 3 hours at room temperature. The dialyzed sample was then frozen and lyophilized and resuspended in 50uL of 0.5M triethylammonium buffer (pH 8.5). Protein concentrations were measured using the Bradford assay.

Details of the iTRAQ labeling procedure have been previously published elsewhere (19). In summary, equivalent amounts of protein for each sample were prepared for labeling according to the iTRAQ manufacturer instructions except

incubation time during labeling was increased to 2 hours. After labeling was completed, the samples were combined and vacuum dried. The combined sample was cleaned with a 4-ml Extract Clean C18 SPE cartridge, and the eluent was dried in vacuo.

D.   Offline fractionation and mass spectrometry

The methods for fractionation and analysis are detailed elsewhere (19). Briefly, the iTRAQ 8-plex sample was resuspended in buffer A and fractionated offline by high pH reverse phase chromatography. Fractions were collected every 2 min and monitored by ultraviolet light absorbance at 215 and 280 nm. Peptide-containing fractions were divided into two equal numbered groups: early and late. The first early fraction was concatenated with the first late fraction, and so on. Concatenated samples were vacuum dried and resuspended in loading solvent and were run on a Velos Orbitrap mass spectrometer (Thermo Fisher Scientific, Waltham, MA) following protocol described in Lin-Moshier et al (20) with the exception that the HCD activation energy was 40 ms.

The mass spectrometer data were analyzed using ProteinPilot 4.5 (AB Sciex, Foster City, CA), a proteomic software program that utilizes the Paragon scoring algorithm to provide confidence levels for protein hits and the ProGroup algorithm tool to group-related and homologous proteins. ProteinPilot searches were performed against the UniProt human database (taxon 9606; March 13, 2013 version) to which a contaminant database (thegpm.org/crap/index, 109 proteins) was appended. Search parameters were cysteine MMTS, iTRAQ 8plex

(peptide labeled), trypsin, and instrument Orbi MS (1–3 ppm) Orbi MS/MS;

biases corrections were applied to account for biological modifications including

systematic errors in protein amount among samples, thorough search effort, and

local 10% False Discovery Rate analysis (with reversed database).

E.   **Statistical Analysis**

For the discovery analysis of the cross-sectional cohort, we analyzed all

the iTRAQ experiments together using mixed models in SAS 9.4 (21-23). The

ProteinPilot peptide data from each iTRAQ experiment are combined,

normalized, and then analyzed using SAS 9.4. To normalize the data and

account for biological and experimental variations such as sample loading,

labeling efficiency, sample mixing, and other technical biases introduced during

the sample analysis, we used an ANOVA model with logarithmic conversion of

the ion peak areas to convert from multiplicative model to an additive model (23).

After that, we analyzed the normalized data by fibrosis group (none, mild,

moderate/severe) for each identified protein to obtain a list of p-values for the

experiment. Due to multiple testing, we adjusted the p-values using the false

discovery rate (FDR) to control the estimated number of false positives among

those considered significant by their raw p-value (21). For the discovery analysis,

we used an FDR of 10%.

In the longitudinal analysis of the prospective cohort, we used the calculated abundance ratios of iTRAQ reporter ions between each prospective sample and the same control sample from a healthy individual. We used the two-sample unpaired Students t-test to test the association between early urine biomarker levels and the outcome of doubling of cortical interstitial volume. Gene ontology and pathway analysis was conducted with the Database for Annotation, Visualization, and Integrated Discovery v6.7. (24, 25).

III. RESULTS

A. Cross-Sectional Cohort

Samples from the cross-sectional cohort were chosen based on their biopsy findings. Using the Banff 1997 criteria for interstitial fibrosis (ci score), eight individuals were chosen for minimal fibrosis (ci0), mild fibrosis (ci1), and moderate to severe fibrosis (ci2 and ci3). The clinical characteristics of these individuals are shown in Table I. The demographics and transplant characteristics were similar between the groups except for the eGFR that was progressively worse with increasing severity of fibrosis.

TABLE I: CROSS-SECTIONAL COHORT CHARACTERISTICS

	Minimal Fibrosis	Mild Fibrosis	Moderate/Severe Fibrosis	P-value
Age (at Transplant)	45.0 (18.5)	44.9 (16.8)	41.8 (18.0)	0.67
Male (%)	88%	75%	50%	0.40
White (%)	88%	75%	100%	0.75
BMI	27.2 (4.3)	25.8 (11.2)	27.4 (8.3)	0.89
Living Donor	75%	75%	75%	1.00
DGF (%)	13%	0%	25%	0.75

B. Cross-Sectional Analysis

The 24 individuals used in the cross-sectional analysis were randomly split between 4 different iTRAQ experiments with two from each category of fibrosis

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combined with 2 control samples for a total of 8 per experiment. For protein identification using iTRAQ, there are two types of false discovery rates (FDR), a global and local FDR. A global FDR indicates the level of confidence for the entire dataset while the local FDR indicates the likelihood the individual protein is incorrect (26). Using a global FDR of 1%, we identified 814, 818, 798, and 709 proteins in the 4 experiments. For a local FDR of 10% we identified 796, 811, 781, and 685 proteins among these experiments.

Analysis of the normalized peptide datasets yielded 1668 proteins that were advanced for differential analysis. Using the Benjamini and Hochberg FDR of 10% with a raw p-value cutoff of <0.0030, the total number of differentially expressed proteins was 227 with 48 between no fibrosis and mild fibrosis, 179 between no fibrosis and moderate/severe fibrosis, and 112 between mild fibrosis and moderate/severe fibrosis. There are 27 common proteins that were differentially expressed between the no fibrosis-mild fibrosis and the mild-moderate/severe group, 25 between the no fibrosis-moderate/severe group and the mild-moderate/severe group, and 70 proteins between the no fibrosis-moderate/severe group and the mild fibrosis-moderate/severe group. In the mild group, 17 of 47 proteins were overexpressed while the severe group had 24 of the 178 proteins that were overexpressed (Table IV, APPENDIX A). In the comparison between the mild group and the moderate/severe group, there were 48 of 111 proteins that were overexpressed. Among all the overexpressed proteins, 21 were present in both the no fibrosis-moderate/severe fibrosis and

mild fibrosis-moderate/severe fibrosis groups while 15 were present in both the no fibrosis-mild fibrosis and mild fibrosis-moderate/severe fibrosis groups.

More proteins were underexpressed in the fibrotic groups compared to the no fibrosis groups (Table V, APPENDIX A). Between the no fibrosis group and the moderate/severe fibrosis group, 154 proteins were underexpressed in the no fibrosis group and were associated with biological processes such as catabolic processes, response to wounding, cell adhesion, and many others while the lysozyme, glycosaminoglycan degradation, renin-angiotensin system pathways were overrepresented. Among the no fibrosis/mild fibrosis group, response to nutrient levels and extracellular stimulus were the biological processes overrepresented in this group while the lysosome pathway was significantly enriched. Finally, when comparing the mild fibrosis to the moderate/severe fibrosis, biological processes including polysaccharide processes and lysosome organization were represented while the lysosome and glucosaminoglycan and other glycan degradation and glutathione metabolism pathways were significantly enriched.

C.   <u>Prospective Cohort</u>

From the ABCAN study, 7 individuals were chosen for proteomic analysis. Using cortical interstitial volume expansion between the two protocol biopsies, we selected 3 individuals with no significant change in volume while 4 had doubled their cortical interstitial volume. The characteristics of these individuals are shown in Table II. Overall, the progressor and non-progressor group were similar except there were no females in the progressor group. Each individual

had urine samples collected at the start of the study and yearly thereafter. We
were able to use either the baseline or first year urine sample as the first
specimen in 6 of the 7 individuals while we started with the second year
specimen in 1 individual. The same two healthy controls were used in each
iTRAQ experiment to allow for comparison between experiments.

TABLE II: BASELINE CHARACTERISTICS OF THE LONGITUDINAL COHORT (NP – NON-PROGRESSOR, P-PROGRESSOR)

Subject	NP1	NP2	NP3	P1	P2	P3	P4
Age (Years)	50.4	58.9	27.7	42.6	69.2	62.3	59.6
Gender	Female	Female	Male	Male	Male	Male	Male
Race	White	Black	White	Hispanic	Asian	White	White
Body Mass Index (kg/m2)	24.3	39.3	20.1	32.9	20.6	24.4	24.1
Donor Type	Cadaver	Living	Living	Cadaver	Living	Living	Cadaver
Diabetic	No	Yes	No	No	Yes	No	Yes
Serum Creatinine (mg/dL)	0.9	1.0	2.0	1.6	1.1	2.1	1.3
Estimated GFR (mL/min/ 1.73m2)	78.2	80.1	45.9	55.0	80.2	35.4	64.6
Measured GFR (mL/min/ 1.73m2)	77.6	51.0	46.4	51.7	51.3	55.6	51.2
Urine Albumin/ Creatinine Ratio (mg/g Creatinine)	6.0	24.1	150.9	140.0	8.8	163.1	4.5

D.   Prospective Analysis

Compared to the cross-sectional analysis where the data were normalized across all experiments and then analyzed by peptide expression, we used the ratio of each identified protein between the transplant patient and the healthy control.

Using the overexpressed proteins from the cross-sectional studies, we compared baseline ratio of each protein between the two groups using the Students t-test after log-transformation of the protein ratios. Of the 55 proteins that were selected for further analysis from the cross-sectional study, 28 were found in 6 of the 7 individuals from the longitudinal cohort. Of these 28 proteins, 5 were significantly different with a p-value < 0.05 and another 3 with a p-value <0.10 (Table III). These included alpha-2-macroglobulin (cytokine, complement component, and serine protease inhibitor), pigment epithelium-derived factor (serine protease inhibitor), retinol-binding protein 4 (transfer/carrier protein), immunoglobulin J chain, apolipoprotein A-IV (lipid transport) and apolipoprotein C-III (transporter, signaling molecule), profilin-1, and alpha-1-acid glycoprotein. The biological processes represented by these proteins include lipid transport and localization, lipid metabolism, and acute inflammatory response.

TABLE III: RESULTS OF THE DISCOVERY CANDIDATE BIOMARKERS IN THE PROSPECTIVE COHORT

Protein	Non-Progressor Mean (95% CI)	Progressor Mean (95% CI)	p-value
alpha-2-macroglobulin	1.10 (0.32-1.88)	2.56 (1.27-3.84)	0.014
pigment epithelium-derived factor	1.05 (0.60-1.51)	2.11 (1.09-3.14)	0.016
retinol-binding protein 4	0.79 (-0.01-1.58)	1.78 (0.98-2.59)	0.031
immunoglobulin J chain	0.48 (0.05-0.91)	0.91 (0.59-1.23)	0.032
apolipoprotein A-IV	1.38 (1.15-1.61)	2.31 (1.39-3.24)	0.043
apolipoprotein C-III	1.48 (1.14-1.82)	2.53 (1.33-3.74)	0.069
profilin-1	1.53 (0.38-2.69)	2.25 (1.67-2.82)	0.076
alpha-1-acid glycoprotein 1	1.34 (-1.20-3.89)	4.32 (0.68-7.96)	0.094
hemopexin	1.05 (0.45-1.64)	1.74 (0.67-2.80)	0.154
fibrinogen alpha chain isoform alpha-E	1.35 (0.68-2.02)	0.93 (0.35-1.50)	0.155
beta-2-microglobulin	1.77 (-1.62-5.15)	4.79 (-0.53-10.11)	0.207
cystatin-M	2.09 (-0.04-4.21)	1.47 (0.83-2.10)	0.250
plasminogen isoform 1	1.31 (0.08-2.54)	2.24 (0.25-4.23)	0.285
complement C3	1.18 (0.63-1.74)	1.76 (0.36-3.16)	0.324
transthyretin	2.08 (-3.00-7.16)	3.70 (0.53-6.87)	0.344
guanylin	1.37 (-0.17-2.92)	1.02 (0.39-1.65)	0.416
immunoglobulin lambda-like polypeptide 5 isoform 1	1.55 (-1.94-5.03)	2.60 (-0.07-5.27)	0.421
alpha-2-HS-glycoprotein	1.06 (-1.17-3.29)	1.53 (0.32-2.74)	0.490
haptoglobin isoform 1	0.36 (-0.42-1.14)	0.26 (0.12-0.39)	0.534
vitronectin	1.21 (0.33-2.10)	1.39 (0.72-2.06)	0.591
cystatin-C	0.90 (0.65-1.16)	0.96 (0.73-1.18)	0.608
keratin, type I cytoskeletal 18	1.20 (-5.51-7.91)	1.45 (0.72-2.19)	0.620
lysozyme C	3.23 (-2.53-9.00)	2.41 (-0.91-5.73)	0.623
complement C4-B-like	1.43 (-4.69-7.55)	1.66 (0.88-2.45)	0.648
histidine-rich glycoprotein	1.93 (-1.14-5.00)	2.23 (0.49-3.96)	0.751
keratin, type II cytoskeletal 8 isoform 2	1.50 (-0.27-3.28)	1.38 (0.90-1.85)	0.756
apolipoprotein A-I	1.90 (0.40-3.41)	1.83 (-0.17-3.84)	0.932
complement factor B	2.24 (-0.82-5.30)	2.27 (0.67-3.86)	0.977

IV.   DISCUSSION

Prediction of IFTA in kidney transplant recipients can have a tremendous impact on allograft survival. Earlier identification can lead to alterations in medications or medical management that could lead to improved overall graft survival.

In this study, we conducted a discovery and validation study looking for novel urine biomarkers of interstitial fibrosis/tubular atrophy in kidney transplant recipients. From our discovery portion using the cross-sectional cohort, we found 55 proteins that were overexpressed between different stages of fibrosis. When these 55 proteins were validated in the longitudinal cohort, 8 were found to predict those that were going to progress, 5 of which with a p-value <0.05.

The proteins identified in our discovery cohort covered a wide range of biological processes include wound healing, lipid metabaolism, and cell adhesion suggesting multiple processes that are involved in renal fibrosis. Several of the proteins discovered in the cross-sectional analysis have been seen in other studies of kidney disease. Urinary cystatin C has been widely studied in kidney disease and kidney transplantation as a biomarker of kidney injury, especially as a biomarker of proximal tubular injury (27, 28). Within the same family of cysteine protease inhibitors, cystatin B and cystatin M are upregulated in early diabetic nephropathy (29) and chronic kidney disease (CKD) (30). Also seen in our discovery analysis were neutrophil gelatinase-associated lipocalin (NGAL) and beta-2 microglobulin, both frequently studied as a biomarker of kidney disease and kidney injury (14, 31).

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Unbiased discovery analysis of biomarkers with proteomics allows for consideration of non-traditional pathways of disease that can then be used to generate new hypotheses. In this study our initial discovery analysis yielded 55 proteins that were associated with increasing degrees of fibrosis. In a similar type of discovery analysis of those with diabetic nephropathy (32), 7 of 55 proteins in our non-diabetic, post-transplant cohort were also seen in their cohort, including alpha-2-HS-glycoprotien, complement C3, hemopexin and haptoglobin, suggesting some overlap in biomarkers of renal dysfunction over a spectrum of a diseases. Conversely, there were many proteins that did not overlap between studies which could be attributed to the heterogeneity in populations, the underlying disease state, differences in analytic methodologies, or even the chance of type I error associated with multiple hypotheses testing despite controlling for a low FDR. In addition, cross-sectional studies can only show associations between biomarkers and diseases and cannot be used to know which biomarkers can predict disease before it occurs. Therefore, we then conducted a validation study in a prospective cohort of kidney transplant recipients that reached our outcomes of interest, specifically a doubling of cortical interstitial volume as a surrogate of IF/TA. Of the 55 proteins, we were able to narrow the candidate biomarkers to 8 that were able to differentiate between progressors and non-progressors of IF/TA.

Of the 8 candidate biomarkers that were validated in the prospective cohort, none have any reported associations with fibrosis. All of these biomarkers are associated with the tubules suggesting tubular injury may play a role in their

urinary expression. Alpha-1-acid glycoprotein 1 has been shown to be upregulated in CKD (33, 34) and can be used in a panel of biomarkers to detect lupus nephritis activity and specific subtypes (35). Alpha-2-macroglobulin is associated with acute tubular injury as seen in tubulitis in kidney transplant recipients (36) and is inversely correlated with lower eGFR in chronic kidney disease (37). Apolipoprotein A-IV has been shown to be filtered by the glomerulus and is reabsorbed by the proximal tubular cells (38). Apolipoprotein C-III has been isolated in the renal tubule but its significance in the urine is unclear (39). Pigment epithelium derived factor has anti-fibrotic properties and has been shown to reduce the damage done by hyperglycemia in diabetic nephropathy (40). Profilin-1 has been associated with renal cell carcinoma and has been isolated in tubular cells but its role in kidney disease is unclear (41). Urine retinol binding protein 4 expression is often considered a biomarker of tubular injury and often associated with Fanconi syndrome where urinary levels are greater than 100 fold higher than normal (42). As for immunoglobulin J chain, it's unclear what its role is in the kidney and fibrosis. Since IF/TA includes tubular atrophy, it is plausible that these biomarkers may be indicative of early tubular damage prior to any histological findings seen on the early protocol biopsies.

There are some significant limitations to this study. First, the discovery analysis approach of a large number of proteins increases the risk of capturing random fluctuations leading to false positive results. To address this, we used a relatively stringent criteria early on in the discovery phase by controlling the FDR rate at 10% with an adjusted p-value. With our initial discovery of 55 proteins, a

FDR rate of 10% would mean that 5.5 or 6 proteins are expected to be false positives among the 55 chosen by the adjusted p-value. Certainly, with the heterogeneity between datasets, the remaining 47 proteins that were trimmed down could be attributed to differences in the patient populations such as race, cause of renal disease, immunosuppression and other medications, etc. The small sample size in the validation group could also explain why many of the proteins were not predictive despite large fold changes in the discovery cohort. Validation in a larger sample cohort with the 55 proteins are needed to confirm that the remaining proteins are not predictive of IF/TA. Finally, we were not able to assess the added benefit of these biomarkers in predicting IF/TA compared to traditional risk factors due to the small sample size. In CKD, typical risk factors for CKD progression include albuminuria and lower eGFR. In kidney transplantation, the use of calcineurin-inhibitors and diabetes may also accelerate IF/TA. A larger cohort is needed to adjust for the appropriate risk factors and better assess the added clinical benefit to these clinical biomarkers.

In summary, proteomic methods can be used to identify novel biomarkers of IF/TA. We identified 55 candidate biomarkers in a discovery analysis and then validated 8 novel biomarkers in an independent population. Further studies in a larger prospective cohort are needed to assess the validity of these candidate biomarkers and the net benefit in clinical practice over traditional risk factors for IF/TA.

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APPENDIX A

TABLE IV: UPREGULATED PROTEINS BETWEEN IF/TA GROUPS

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value*
alpha-1-acid glycoprotein 1	167857790	1.43 (1.12-1.81)	<0.0001	0.82 (0.64-1.04)	0.0164	0.57 (0.45-0.73)	<0.0001
alpha-2-HS-glycoprotein	156523970	0.87 (0.61-1.25)	0.2886	1.29 (0.90-1.85)	0.0428	1.48 (1.03-2.12)	0.002
alpha-2-macroglobulin	66932947	0.79 (0.58-1.06)	0.023	1.11 (0.82-1.50)	0.3244	1.41 (1.05-1.90)	0.0011
apolipoprotein A-I	4557321	0.59 (0.41-0.86)	<0.0001	1.24 (0.85-1.81)	0.0998	2.11 (1.45-3.06)	<0.0001
apolipoprotein A-IV	71773110	0.69 (0.48-0.99)	0.0037	1.47 (1.02-2.12)	0.003	2.14 (1.48-3.09)	<0.0001
apolipoprotein B-100	105990532	1.05 (0.65-1.68)	0.7879	2.30 (1.43-3.68)	<0.0001	2.19 (1.37-3.51)	<0.0001
apolipoprotein C-III	4557323	0.59 (0.29-1.23)	0.045	2.06 (1.00-4.25)	0.0054	3.48 (1.68-7.24)	<0.0001
beta-2-microglobulin	4757826	1.51 (0.97-2.34)	0.0083	2.61 (1.68-4.05)	<0.0001	1.73 (1.11-2.69)	0.0005
calcium-activated chloride channel regulator 1	110611231	3.59 (1.45-8.88)	0.0001	1.00 (0.39-2.56)	0.9894	0.28 (0.11-0.71)	0.0002
coactosin-like protein	21624607	0.91 (0.47-1.76)	0.6933	1.89 (0.98-3.67)	0.0069	2.07 (1.07-4.04)	0.0022
collectin-12	18641360	0.67 (0.44-1.03)	0.0085	1.18 (0.77-1.81)	0.267	1.76 (1.15-2.70)	0.0002
complement C3	115298678	0.66 (0.56-0.79)	<0.0001	1.15 (0.97-1.38)	0.0208	1.74 (1.46-2.07)	<0.0001
complement C4-B-like	338858017	1.29 (0.68-2.45)	0.2587	2.60 (1.37-4.93)	<0.0001	2.01 (1.06-3.81)	0.0026
complement C5	38016947	0.61 (0.33-1.13)	0.0246	1.19 (0.64-2.22)	0.4216	1.96 (1.05-3.64)	0.0026
complement component C8 gamma chain	166197660	0.75 (0.38-1.45)	0.215	2.20 (1.14-4.25)	0.0008	2.95 (1.52-5.74)	<0.0001

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value*
complement component C9	4502511	0.96 (0.61-1.52)	0.8112	1.69 (1.07-2.67)	0.0014	1.76 (1.11-2.78)	0.0006
complement factor B	67782358	0.89 (0.56-1.41)	0.4649	1.72 (1.08-2.74)	0.001	1.94 (1.22-3.09)	<0.0001
complement factor D	42544239	1.15 (0.65-2.03)	0.4994	2.35 (1.32-4.16)	<0.0001	2.05 (1.16-3.61)	0.0004
complement factor H isoform a	62739186	0.86 (0.57-1.30)	0.3127	1.66 (1.10-2.50)	0.0005	1.92 (1.27-2.90)	<0.0001
connective tissue growth factor	4503123	0.99 (0.55-1.78)	0.9725	2.24 (1.24-4.04)	0.0001	2.26 (1.25-4.09)	0.0002
cystatin-B	4503117	1.08 (0.56-2.08)	0.7266	2.06 (1.07-3.97)	0.0023	1.90 (0.99-3.66)	0.0065
cystatin-C	4503107	0.84 (0.51-1.36)	0.2995	1.76 (1.08-2.85)	0.0011	2.10 (1.29-3.42)	<0.0001
cystatin-M	4503113	0.91 (0.53-1.56)	0.6142	1.87 (1.09-3.20)	0.001	2.06 (1.20-3.53)	0.0002
desmocollin-1 isoform Dsc1a	13435361	1.39 (0.74-2.60)	0.1458	2.08 (1.11-3.89)	0.0012	1.50 (0.80-2.82)	0.0701
fibrinogen alpha chain isoform alpha-E	4503689	0.68 (0.49-0.93)	0.0006	0.97 (0.70-1.33)	0.7863	1.43 (1.04-1.97)	0.0016
fibrinogen gamma chain isoform gamma-B	70906439	0.88 (0.58-1.34)	0.3846	1.38 (0.90-2.10)	0.0317	1.57 (1.03-2.38)	0.0025
guanylin	38176149	0.74 (0.39-1.39)	0.1769	1.45 (0.77-2.75)	0.0985	1.97 (1.04-3.74)	0.003
haptoglobin isoform 1	4826762	0.36 (0.28-0.46)	<0.0001	0.93 (0.72-1.19)	0.3854	2.56 (2.00-3.28)	<0.0001
hemopexin	11321561	0.86 (0.69-1.07)	0.0556	1.29 (1.04-1.61)	0.0009	1.50 (1.21-1.87)	<0.0001
histidine-rich glycoprotein	4504489	0.67 (0.41-1.09)	0.0206	1.14 (0.70-1.87)	0.448	1.71 (1.05-2.80)	0.0022
IgGFc-binding protein	154146262	3.77 (1.83-7.73)	<0.0001	0.72 (0.35-1.50)	0.2092	0.19 (0.09-0.40)	<0.0001
immunoglobulin J chain	21489959	1.95 (1.05-3.63)	0.0026	0.76 (0.41-1.42)	0.218	0.39 (0.21-0.73)	<0.000

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value*
							1
immunoglobulin lambda-like polypeptide 5 isoform 1	295986608	1.22 (0.88-1.69)	0.0899	1.43 (1.03-1.99)	0.0023	1.17 (0.84-1.63)	0.1736
insulin-like growth factor-binding protein 6	11321593	0.89 (0.53-1.49)	0.5251	1.83 (1.10-3.07)	0.001	2.06 (1.23-3.45)	<0.0001
inter-alpha-trypsin inhibitor heavy chain H4 isoform 2	262050538	0.68 (0.41-1.13)	0.0328	1.19 (0.72-1.98)	0.3296	1.75 (1.05-2.91)	0.002
keratin, type I cytoskeletal 13 isoform a	131412225	0.48 (0.16-1.41)	0.0599	1.99 (0.71-5.59)	0.0651	4.12 (1.41-12.06)	0.0004
keratin, type I cytoskeletal 18	4557888	4.29 (1.36-13.54)	0.0008	1.46 (0.46-4.60)	0.357	0.34 (0.11-1.07)	0.0105
keratin, type II cytoskeletal 8 isoform 2	4504919	2.82 (1.11-7.16)	0.002	1.04 (0.41-2.65)	0.8992	0.37 (0.15-0.91)	0.0021
lysozyme C	4557894	1.19 (0.70-2.01)	0.3556	3.02 (1.79-5.10)	<0.0001	2.54 (1.50-4.31)	<0.0001
myeloblastin	71361688	2.71 (1.11-6.64)	0.0021	0.64 (0.26-1.58)	0.1636	0.23 (0.10-0.58)	<0.0001
myeloperoxidase	4557759	2.39 (1.33-4.31)	<0.0001	0.56 (0.31-1.02)	0.0068	0.23 (0.13-0.43)	<0.0001
neutrophil gelatinase-associated lipocalin	38455402	1.77 (1.05-2.98)	0.0022	1.02 (0.60-1.72)	0.9187	0.58 (0.34-0.98)	0.0032
oxytocin-neurophysin 1	4505537	0.75 (0.21-2.70)	0.5297	4.68 (1.30-16.88)	0.0027	6.25 (1.73-22.56)	0.0006
pigment epithelium-derived factor	39725934	0.93 (0.59-1.45)	0.6257	1.88 (1.20-2.92)	<0.0001	2.02 (1.30-3.16)	<0.0001
plasminogen isoform 1	4505881	0.86 (0.67-1.10)	0.0857	1.22 (0.95-1.56)	0.0229	1.42 (1.11-1.81)	<0.0001
profilin-1	4826898	1.15 (0.59-2.24)	0.5631	2.49 (1.28-4.84)	0.0001	2.17 (1.11-4.24)	0.0012
protein disulfide-isomerase	20070125	7.83 (2.20-	<0.0001	1.65 (0.49-5.59)	0.2537	0.21 (0.06-0.75)	0.0013

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value*	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value*
		27.91)					
protein FAM3C	91807125	1.18 (0.66-2.10)	0.4211	1.92 (1.08-3.41)	0.0016	1.62 (0.91-2.90)	0.018
proteoglycan 4 isoform A	67190163	0.93 (0.49-1.77)	0.7617	2.02 (1.06-3.84)	0.0023	2.16 (1.14-4.12)	0.0008
retinol-binding protein 4	55743122	1.16 (0.85-1.57)	0.177	2.54 (1.88-3.45)	<0.0001	2.20 (1.62-2.99)	<0.0001
small proline-rich protein 3	4885607	0.62 (0.36-1.07)	0.0147	1.16 (0.67-2.00)	0.452	1.87 (1.07-3.25)	0.0017
thymosin beta-4	11056061	0.82 (0.35-1.94)	0.5147	3.06 (1.29-7.27)	0.0003	3.74 (1.54-9.08)	<0.0001
transthyretin	4507725	0.68 (0.52-0.90)	<0.0001	1.16 (0.88-1.53)	0.1308	1.70 (1.29-2.24)	<0.0001
vitamin D-binding protein isoform 3	324021745	0.72 (0.54-0.96)	0.0011	1.02 (0.77-1.37)	0.8256	1.43 (1.07-1.91)	0.0005
vitronectin	88853069	0.73 (0.55-0.97)	0.0018	1.01 (0.76-1.35)	0.9068	1.39 (1.04-1.86)	0.0012

*p-value of less than 0.003 for a FDR 10%

TABLE V: UNDEREXPRESSED PROTEINS BETWEEN IF/TA GROUPS

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
14-3-3 protein zeta/delta	4507953	1.20 (0.65-2.21)	0.4114	0.61 (0.33-1.12)	0.0231	0.51 (0.27-0.94)	0.0022
2'-5'-oligoadenylate synthase 3	45007007	0.39 (0.30-0.50)	0.0018	0.39 (0.30-0.50)	0.0018	1.00 (0.77-1.29)	0.9865
4F2 cell-surface antigen heavy chain isoform b	61744477	1.89 (0.63-5.72)	0.1097	0.46 (0.15-1.38)	0.0516	0.24 (0.08-0.73)	0.0007
4F2 cell-surface antigen heavy chain isoform c	65506891	0.75 (0.33-1.69)	0.3172	0.37 (0.16-0.84)	0.0008	0.49 (0.22-1.12)	0.0161
acid ceramidase isoform a	189011548	1.09 (0.64-1.85)	0.6366	0.51 (0.30-0.86)	0.0004	0.47 (0.27-0.79)	<0.0001
actin, cytoplasmic 1	4501885	0.69 (0.39-1.20)	0.0569	0.51 (0.29-0.89)	0.0007	0.74 (0.42-1.29)	0.1287
actin, cytoplasmic 2	4501887	0.98 (0.61-1.59)	0.9239	0.52 (0.32-0.85)	0.0002	0.53 (0.33-0.86)	0.0003
adenosylhomocysteinase isoform 1	9951915	0.67 (0.27-1.63)	0.2192	0.31 (0.13-0.76)	0.0022	0.47 (0.19-1.15)	0.0302
ADP-ribosylation factor 1	66879664	0.45 (0.17-1.17)	0.0275	0.20 (0.08-0.51)	<0.0001	0.43 (0.17-1.12)	0.0215
afamin	4501987	0.72 (0.56-0.92)	0.0002	0.72 (0.56-0.92)	0.0002	1.00 (0.77-1.29)	0.9802
alpha-amylase 1	56549664	0.62 (0.33-1.19)	0.0391	0.41 (0.21-0.80)	0.0002	0.66 (0.34-1.29)	0.0821
alpha-amylase 2B	10280622	0.61 (0.33-1.12)	0.0242	0.40 (0.21-0.75)	<0.0001	0.65 (0.35-1.22)	0.0558
alpha-enolase isoform 1	4503571	0.89 (0.52-1.52)	0.5294	0.53 (0.31-0.90)	0.0009	0.59 (0.35-1.02)	0.0068
alpha-N-acetylglucosaminidase	66346698	0.82 (0.57-1.20)	0.1433	0.39 (0.27-0.57)	<0.0001	0.47 (0.33-0.69)	<0.0001
aminopeptidase N	157266300	0.93 (0.73-1.18)	0.3909	0.46 (0.36-0.58)	<0.0001	0.49 (0.39-0.62)	<0.0001
angiotensin-converting enzyme 2	11225609	0.71 (0.34-1.48)	0.1912	0.44 (0.21-0.91)	0.0018	0.61 (0.29-1.28)	0.062
annexin A4	4502105	0.83 (0.42-1.61)	0.4218	0.47 (0.24-0.92)	0.002	0.57 (0.29-1.11)	0.0193
annexin A5	4502107	0.78 (0.43-1.42)	0.2384	0.42 (0.23-0.76)	<0.0001	0.54 (0.29-0.98)	0.0037

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
annexin A7 isoform 2	4809279	0.90 (0.55-1.47)	0.5436	0.46 (0.28-0.76)	<0.0001	0.52 (0.32-0.85)	0.0003
apolipoprotein D	4502163	0.65 (0.45-0.92)	0.0005	0.38 (0.27-0.54)	<0.0001	0.59 (0.41-0.84)	<0.0001
arylsulfatase A isoform a	313569797	0.76 (0.42-1.35)	0.1704	0.52 (0.29-0.93)	0.0017	0.69 (0.39-1.24)	0.0736
attractin isoform 1	21450861	0.81 (0.47-1.38)	0.268	0.56 (0.33-0.96)	0.0026	0.69 (0.40-1.18)	0.0539
azurocidin	11342670	2.71 (0.90-8.12)	0.012	0.58 (0.19-1.75)	0.1691	0.22 (0.07-0.62)	<0.0001
basigin isoform 2	38372925	0.73 (0.35-1.53)	0.2361	0.42 (0.20-0.88)	0.0013	0.58 (0.28-1.20)	0.0362
beta-galactosidase isoform a	119372308	0.60 (0.38-0.96)	0.0021	0.39 (0.24-0.62)	<0.0001	0.64 (0.40-1.03)	0.0078
beta-galactosidase isoform b	119372312	1.13 (0.60-2.13)	0.5861	0.40 (0.22-0.76)	<0.0001	0.36 (0.19-0.67)	<0.0001
beta-glucuronidase	268834192	0.72 (0.42-1.23)	0.085	0.33 (0.19-0.57)	<0.0001	0.46 (0.27-0.80)	<0.0001
beta-hexosaminidase subunit alpha	189181666	0.73 (0.46-1.15)	0.0521	0.42 (0.27-0.67)	<0.0001	0.58 (0.37-0.92)	0.001
beta-hexosaminidase subunit beta	4504373	0.85 (0.47-1.51)	0.4151	0.42 (0.23-0.74)	<0.0001	0.49 (0.28-0.88)	0.0007
beta-mannosidase	84798622	0.84 (0.43-1.65)	0.4839	0.43 (0.22-0.84)	0.0014	0.51 (0.26-1.00)	0.0085
bile salt-activated lipase	148536848	0.83 (0.45-1.52)	0.3774	0.47 (0.25-0.87)	0.0007	0.57 (0.30-1.06)	0.0109
butyrophilin subfamily 2 member A1 isoform 1	5921461	0.93 (0.60-1.43)	0.6276	0.53 (0.34-0.82)	<0.0001	0.57 (0.37-0.88)	0.0003
cadherin-1	4757960	0.72 (0.49-1.05)	0.0139	0.63 (0.43-0.92)	0.0006	0.87 (0.59-1.28)	0.3153
cadherin-2	14589889	0.64 (0.31-1.33)	0.0873	0.46 (0.22-0.95)	0.0027	0.71 (0.34-1.47)	0.1869
cadherin-6	4826673	1.27 (0.70-2.29)	0.2599	0.65 (0.36-1.18)	0.0428	0.51 (0.28-0.93)	0.0018
calcium-binding protein 39	7706481	0.78 (0.39-1.58)	0.334	0.28 (0.14-0.56)	<0.0001	0.36 (0.18-0.72)	0.0001
calreticulin	4757900	1.64 (0.93-2.87)	0.0138	0.82 (0.47-1.44)	0.3196	0.50 (0.29-0.88)	0.0006
carbonic anhydrase 2	4557395	0.81 (0.41-1.59)	0.3721	0.40 (0.20-0.79)	0.0004	0.50 (0.25-0.98)	0.0055
carboxypeptidase M	6631081	0.69 (0.45-1.07)	0.0171	0.46 (0.30-0.71)	<0.0001	0.67 (0.43-1.03)	0.0088
carboxypeptidase N subunit 2	256217721	0.73 (0.44-1.22)	0.0851	0.58 (0.34-0.97)	0.0028	0.79 (0.47-1.32)	0.1967

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
carboxypeptidase Q	7706387	0.79 (0.46-1.35)	0.2143	0.43 (0.25-0.74)	<0.0001	0.54 (0.32-0.93)	0.0016
carcinoembryonic antigen-related cell adhesion molecule 7	5901930	8.13 (1.68-39.22)	0.0055	0.55 (0.10-2.99)	0.3443	0.07 (0.01-0.37)	0.002
cathepsin D	4503143	0.63 (0.46-0.86)	<0.0001	0.54 (0.40-0.74)	<0.0001	0.87 (0.63-1.18)	0.1941
CD44 antigen isoform 2	48255937	0.80 (0.55-1.15)	0.0774	0.51 (0.35-0.73)	<0.0001	0.64 (0.44-0.92)	0.0006
CD59 glycoprotein	42761474	0.81 (0.54-1.22)	0.1506	0.63 (0.42-0.95)	0.0014	0.78 (0.52-1.16)	0.0772
CD9 antigen	4502693	0.55 (0.24-1.23)	0.043	0.27 (0.12-0.61)	<0.0001	0.50 (0.22-1.12)	0.0208
clusterin	355594753	0.56 (0.40-0.80)	<0.0001	0.71 (0.50-1.01)	0.0056	1.25 (0.88-1.78)	0.0684
collagen alpha-1(I) chain	110349772	0.61 (0.38-0.97)	0.0029	0.67 (0.41-1.07)	0.0163	1.10 (0.68-1.77)	0.5839
collagen alpha-1(III) chain	4502951	0.69 (0.38-1.28)	0.0916	0.51 (0.28-0.95)	0.0023	0.74 (0.40-1.36)	0.1624
collagen alpha-1(VI) chain	87196339	0.69 (0.51-0.93)	0.0006	0.46 (0.34-0.62)	<0.0001	0.67 (0.49-0.90)	0.0002
collagen alpha-1(XII) chain long isoform	93141047	0.77 (0.52-1.15)	0.0667	0.63 (0.42-0.93)	0.001	0.81 (0.54-1.21)	0.1365
collagen alpha-1(XV) chain	116008152	0.83 (0.55-1.27)	0.2208	0.56 (0.37-0.85)	0.0001	0.67 (0.44-1.02)	0.0077
complement C1r subcomponent-like protein	289547636	0.79 (0.48-1.31)	0.1969	0.48 (0.29-0.80)	<0.0001	0.61 (0.37-1.00)	0.0052
complement factor I	119392081	0.61 (0.42-0.88)	0.0002	0.77 (0.53-1.12)	0.0518	1.27 (0.88-1.85)	0.0656
copine-5	25141323	0.39 (0.24-0.64)	0.0004	0.39 (0.24-0.64)	0.0004	1.01 (0.61-1.65)	0.9728
creatine kinase B-type	21536286	0.57 (0.20-1.60)	0.1261	0.31 (0.11-0.87)	0.0019	0.54 (0.19-1.53)	0.0993
cubilin	126091152	0.74 (0.57-0.95)	0.0009	0.56 (0.43-0.72)	<0.0001	0.76 (0.58-0.98)	0.0027
deoxyribonuclease-1	21361254	0.66 (0.38-1.15)	0.0345	0.34 (0.19-0.59)	<0.0001	0.51 (0.29-0.89)	0.0007
di-N-acetylchitobiase	4758092	0.75 (0.46-1.22)	0.0981	0.53 (0.33-0.87)	0.0004	0.71 (0.44-1.16)	0.0508
dipeptidase 1	4758190	0.72 (0.33-1.56)	0.2339	0.32 (0.15-0.70)	<0.0001	0.44 (0.20-0.96)	0.0035
dipeptidyl peptidase 1	189083844	0.88 (0.58-1.34)	0.3923	0.54 (0.35-0.82)	<0.0001	0.61 (0.40-0.93)	0.0009

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
isoform a							
dipeptidyl peptidase 2	62420888	0.85 (0.61-1.20)	0.1834	0.50 (0.36-0.70)	<0.0001	0.59 (0.42-0.82)	<0.0001
dipeptidyl peptidase 4	18765694	1.10 (0.76-1.60)	0.4489	0.64 (0.44-0.92)	0.0007	0.58 (0.40-0.84)	<0.0001
E3 ubiquitin-protein ligase RNF13	6005864	0.57 (0.53-0.62)	0.0002	0.64 (0.59-0.69)	0.0005	1.12 (1.03-1.20)	0.0267
endonuclease domain-containing 1 protein	148225659	0.85 (0.54-1.33)	0.3057	0.54 (0.34-0.84)	0.0001	0.63 (0.41-0.99)	0.0042
endosialin	9966885	0.73 (0.45-1.19)	0.071	0.45 (0.28-0.74)	<0.0001	0.62 (0.38-1.01)	0.0057
endothelial protein C receptor	34335272	0.77 (0.49-1.19)	0.0894	0.37 (0.24-0.58)	<0.0001	0.49 (0.31-0.76)	<0.0001
erythrocyte band 7 integral membrane protein isoform a	38016911	0.81 (0.43-1.52)	0.3399	0.48 (0.25-0.90)	0.0017	0.59 (0.32-1.12)	0.0237
extracellular sulfatase Sulf-2 isoform a	29789100	0.68 (0.42-1.09)	0.0218	0.50 (0.31-0.81)	<0.0001	0.74 (0.46-1.20)	0.0775
ezrin	21614499	0.85 (0.59-1.24)	0.2317	0.52 (0.36-0.75)	<0.0001	0.61 (0.42-0.88)	0.0002
ferritin light chain	20149498	1.31 (0.68-2.54)	0.2471	0.52 (0.27-1.00)	0.0069	0.39 (0.20-0.76)	0.0002
fibronectin isoform 5	47132553	0.42 (0.27-0.65)	<0.0001	0.34 (0.22-0.53)	<0.0001	0.81 (0.52-1.26)	0.1783
filamin-A isoform 2	160420317	0.80 (0.52-1.25)	0.1635	0.59 (0.38-0.92)	0.0008	0.73 (0.47-1.14)	0.0486
folate receptor alpha	9257213	0.70 (0.34-1.44)	0.1658	0.45 (0.22-0.92)	0.0021	0.64 (0.31-1.32)	0.0838
fructose-bisphosphate aldolase B	40354205	0.81 (0.50-1.31)	0.2176	0.58 (0.36-0.94)	0.0016	0.72 (0.44-1.16)	0.0512
galectin-3-binding protein	5031863	0.69 (0.50-0.96)	0.0017	0.43 (0.31-0.60)	<0.0001	0.62 (0.44-0.86)	<0.0001
gamma-glutamyl hydrolase	4503987	0.73 (0.34-1.56)	0.2392	0.42 (0.20-0.91)	0.0017	0.58 (0.27-1.25)	0.0457
gamma-glutamyltranspeptidase 1	73915096	0.78 (0.54-1.11)	0.0478	0.49 (0.34-0.71)	<0.0001	0.64 (0.44-0.91)	0.0004
glutaminyl-peptide cyclotransferase	6912618	0.74 (0.44-1.26)	0.1129	0.48 (0.28-0.81)	0.0001	0.64 (0.38-1.09)	0.019

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
glutamyl aminopeptidase	132814467	0.96 (0.69-1.33)	0.7163	0.47 (0.34-0.65)	<0.0001	0.49 (0.35-0.68)	<0.0001
glutathione S-transferase A1	22091454	0.77 (0.49-1.23)	0.1176	0.48 (0.30-0.77)	<0.0001	0.63 (0.39-1.00)	0.0048
glutathione S-transferase omega-1 isoform 1	4758484	1.42 (1.12-1.80)	0.0253	0.63 (0.50-0.80)	0.0121	0.44 (0.35-0.56)	0.0024
glyoxalase domain-containing protein 4	217330598	0.64 (0.53-0.77)	0.007	0.43 (0.35-0.52)	0.0011	0.67 (0.55-0.81)	0.0092
Golgi membrane protein 1	29550850	0.81 (0.48-1.36)	0.2429	0.55 (0.32-0.92)	0.0013	0.68 (0.40-1.15)	0.0381
G-protein coupled receptor family C group 5 member C isoform b	40217833	0.60 (0.26-1.41)	0.1018	0.34 (0.14-0.78)	0.0009	0.56 (0.24-1.30)	0.0584
group XV phospholipase A2	6912484	0.85 (0.43-1.69)	0.5046	0.40 (0.20-0.79)	0.0003	0.47 (0.23-0.93)	0.0027
guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	20357529	0.81 (0.38-1.75)	0.4476	0.42 (0.19-0.89)	0.0023	0.51 (0.24-1.10)	0.0172
heat shock protein HSP 90-alpha isoform 1	153792590	1.58 (0.82-3.02)	0.0506	0.66 (0.35-1.27)	0.0771	0.42 (0.22-0.81)	0.0003
heat shock protein HSP 90-beta isoform c	431822408	0.45 (0.15-1.32)	0.0539	0.19 (0.07-0.57)	0.0006	0.43 (0.15-1.27)	0.0429
hemoglobin subunit alpha	4504347	0.42 (0.23-0.77)	<0.0001	0.39 (0.21-0.72)	<0.0001	0.94 (0.51-1.73)	0.7848
hemoglobin subunit beta	4504349	0.32 (0.19-0.55)	<0.0001	0.27 (0.16-0.47)	<0.0001	0.86 (0.50-1.48)	0.4395
insulin-like growth factor-binding protein 7 isoform 1	4504619	0.58 (0.36-0.93)	0.0013	0.32 (0.20-0.52)	<0.0001	0.56 (0.34-0.90)	0.0007
integral membrane protein GPR155 isoform 1	74271834	0.73 (0.23-2.30)	0.4433	0.22 (0.07-0.68)	0.0012	0.30 (0.09-0.94)	0.0072
inter-alpha-trypsin inhibitor heavy chain H4 isoform 1	31542984	0.77 (0.59-1.02)	0.0077	0.60 (0.46-0.80)	<0.0001	0.78 (0.59-1.03)	0.0115
isocitrate dehydrogenase	28178825	0.89 (0.49-1.62)	0.5908	0.33 (0.18-0.60)	<0.0001	0.37 (0.21-0.68)	<0.0001

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
[NADP] cytoplasmic							
kallikrein-1	4504875	0.69 (0.36-1.29)	0.0926	0.35 (0.18-0.66)	<0.0001	0.51 (0.27-0.97)	0.0032
lactotransferrin isoform 1	54607120	1.37 (0.92-2.04)	0.0265	0.55 (0.37-0.83)	<0.0001	0.40 (0.27-0.60)	<0.0001
laminin subunit beta-3	62868217	0.51 (0.15-1.70)	0.129	0.21 (0.06-0.70)	0.0014	0.41 (0.12-1.37)	0.0491
leucine-rich alpha-2-glycoprotein	16418467	1.04 (0.71-1.52)	0.7788	0.69 (0.47-1.01)	0.0066	0.67 (0.46-0.98)	0.0028
L-lactate dehydrogenase B chain	4557032	0.80 (0.43-1.48)	0.3017	0.47 (0.25-0.88)	0.0008	0.60 (0.32-1.11)	0.0192
low affinity immunoglobulin gamma Fc region receptor III-A isoform a	50726979	0.70 (0.36-1.37)	0.1354	0.41 (0.21-0.80)	0.0002	0.58 (0.29-1.14)	0.0238
low-density lipoprotein receptor-related protein 2	126012573	0.66 (0.50-0.87)	<0.0001	0.56 (0.43-0.74)	<0.0001	0.85 (0.65-1.12)	0.0995
lymphatic vessel endothelial hyaluronic acid receptor 1	40549451	0.87 (0.51-1.47)	0.4447	0.47 (0.28-0.80)	<0.0001	0.55 (0.32-0.92)	0.0012
lymphocyte function-associated antigen 3 isoform 1	4502677	0.68 (0.28-1.64)	0.2198	0.30 (0.12-0.73)	0.0005	0.44 (0.18-1.07)	0.0137
lysosomal acid phosphatase isoform 1	4557010	0.82 (0.55-1.24)	0.1786	0.43 (0.29-0.65)	<0.0001	0.53 (0.35-0.79)	<0.0001
lysosomal alpha-glucosidase	119393895	0.70 (0.51-0.96)	0.0016	0.42 (0.31-0.59)	<0.0001	0.61 (0.44-0.83)	<0.0001
lysosomal protective protein isoform c	262527235	0.90 (0.56-1.45)	0.5494	0.48 (0.30-0.76)	<0.0001	0.53 (0.33-0.85)	0.0002
lysosome-associated membrane glycoprotein 2 isoform B	7669503	0.38 (0.18-0.82)	0.0005	0.21 (0.10-0.46)	<0.0001	0.55 (0.25-1.21)	0.0345
maltase-glucoamylase,	221316699	0.85 (0.58-1.23)	0.2084	0.46 (0.32-0.67)	<0.0001	0.54 (0.37-0.79)	<0.0001

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
intestinal							
mannan-binding lectin serine protease 2 isoform 1	21264363	1.48 (0.81-2.68)	0.0657	0.48 (0.27-0.88)	0.0007	0.33 (0.18-0.59)	<0.0001
mannosyl-oligosaccharide 1,2-alpha-mannosidase IA	24497519	0.72 (0.46-1.13)	0.0396	0.62 (0.40-0.96)	0.0023	0.85 (0.55-1.33)	0.3104
matrix-remodeling-associated protein 8	14150145	0.82 (0.56-1.20)	0.1411	0.52 (0.35-0.75)	<0.0001	0.63 (0.43-0.91)	0.0005
metalloproteinase inhibitor 2	4507511	0.42 (0.17-1.05)	0.0177	0.26 (0.10-0.65)	0.0008	0.61 (0.24-1.55)	0.1555
migration and invasion enhancer 1	42822891	0.77 (0.37-1.61)	0.3274	0.43 (0.21-0.90)	0.0018	0.56 (0.27-1.16)	0.027
MIT domain-containing protein 1	20270349	0.68 (0.59-0.79)	0.0046	0.53 (0.46-0.61)	0.001	0.77 (0.67-0.89)	0.0136
mucin-1 isoform 2	67189007	0.54 (0.26-1.13)	0.0205	0.36 (0.17-0.76)	0.0002	0.67 (0.32-1.40)	0.1301
N-acetylgalactosamine-6-sulfatase	4503899	0.66 (0.28-1.58)	0.1857	0.31 (0.13-0.74)	0.0002	0.47 (0.20-1.12)	0.0156
N-acetylglucosamine-6-sulfatase	4504061	0.82 (0.56-1.20)	0.1356	0.57 (0.39-0.84)	<0.0001	0.70 (0.48-1.03)	0.0086
neprilysin	116256333	0.66 (0.40-1.07)	0.0164	0.39 (0.24-0.64)	<0.0001	0.59 (0.36-0.98)	0.0033
neurogenic locus notch homolog protein 3	134244285	0.59 (0.26-1.35)	0.0791	0.34 (0.15-0.78)	0.0005	0.58 (0.25-1.32)	0.0653
neuroserpin	4826904	0.56 (0.23-1.38)	0.0747	0.34 (0.14-0.84)	0.0016	0.61 (0.25-1.51)	0.13
non-secretory ribonuclease	4506549	0.78 (0.56-1.10)	0.043	0.64 (0.46-0.90)	0.0003	0.82 (0.58-1.15)	0.0986
NSFL1 cofactor p47 isoform d	332078466	0.54 (0.23-1.27)	0.0538	0.30 (0.13-0.71)	0.0007	0.56 (0.24-1.30)	0.0654
nuclear transport factor 2	5031985	1.02 (0.51-2.07)	0.9313	0.48 (0.24-0.97)	0.0036	0.47 (0.23-0.95)	0.0028
olfactomedin-4	32313593	1.10 (0.66-1.84)	0.6001	0.60 (0.36-1.02)	0.0065	0.55 (0.33-0.92)	0.0012
osteopontin isoform OPN-a	91206462	0.51 (0.23-1.11)	0.0161	0.31 (0.14-0.69)	<0.0001	0.62 (0.28-1.37)	0.0908

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
pancreatic alpha-amylase	4502085	0.44 (0.25-0.77)	<0.0001	0.31 (0.17-0.54)	<0.0001	0.69 (0.39-1.22)	0.0658
pepsin A	119372298	0.61 (0.36-1.04)	0.0096	0.49 (0.29-0.85)	0.0002	0.81 (0.47-1.38)	0.2616
peptidyl-prolyl cis-trans isomerase B	4758950	0.60 (0.30-1.19)	0.037	0.25 (0.13-0.51)	<0.0001	0.42 (0.21-0.85)	0.0007
phosphatidylcholine-sterol acyltransferase	4557892	0.76 (0.47-1.25)	0.1239	0.51 (0.31-0.83)	0.0002	0.67 (0.41-1.09)	0.0232
phosphatidylethanolamine-binding protein 1	4505621	0.72 (0.40-1.30)	0.1205	0.41 (0.23-0.73)	<0.0001	0.56 (0.31-1.00)	0.0054
phosphoinositide-3-kinase-interacting protein 1 isoform 1	51317358	0.77 (0.46-1.31)	0.1686	0.53 (0.31-0.91)	0.001	0.69 (0.40-1.18)	0.0513
phospholipase D3	72534684	0.94 (0.46-1.91)	0.7992	0.45 (0.22-0.91)	0.0019	0.48 (0.23-0.97)	0.0042
plasma alpha-L-fucosidase	40068512	0.98 (0.49-1.94)	0.9238	0.44 (0.22-0.87)	0.0011	0.45 (0.23-0.89)	0.0015
plasma serine protease inhibitor	194018472	0.70 (0.51-0.95)	0.0011	0.40 (0.29-0.55)	<0.0001	0.58 (0.42-0.79)	<0.0001
polymeric immunoglobulin receptor	31377806	0.94 (0.71-1.25)	0.5317	0.68 (0.51-0.90)	0.0001	0.72 (0.54-0.96)	0.0012
probable serine carboxypeptidase CPVL	83641876	0.77 (0.43-1.38)	0.2008	0.52 (0.29-0.94)	0.0021	0.68 (0.38-1.23)	0.0665
pro-epidermal growth factor isoform 2	296011013	0.73 (0.56-0.95)	0.0008	0.42 (0.32-0.55)	<0.0001	0.57 (0.44-0.75)	<0.0001
programmed cell death protein 6 isoform 1	7019485	1.23 (0.50-3.03)	0.5118	0.42 (0.17-1.03)	0.0108	0.34 (0.14-0.83)	0.0021
prolactin-inducible protein	4505821	0.34 (0.19-0.62)	<0.0001	0.24 (0.14-0.43)	<0.0001	0.70 (0.39-1.26)	0.0906
prostasin	4506153	0.82 (0.50-1.36)	0.2755	0.50 (0.30-0.82)	0.0002	0.60 (0.36-1.00)	0.0057
prostate-specific antigen isoform 1	4502173	0.77 (0.48-1.24)	0.1192	0.41 (0.26-0.66)	<0.0001	0.54 (0.33-0.86)	0.0002

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
prostatic acid phosphatase isoform PAP	6382064	1.21 (0.69-2.12)	0.3397	0.45 (0.26-0.80)	<0.0001	0.37 (0.21-0.66)	<0.0001
prostatic acid phosphatase isoform TM-PAP	197116348	0.39 (0.21-0.70)	<0.0001	0.18 (0.10-0.33)	<0.0001	0.47 (0.26-0.85)	0.0003
proteasome subunit beta type-2 isoform 1	4506195	0.51 (0.19-1.35)	0.0817	0.25 (0.09-0.65)	0.0028	0.48 (0.18-1.28)	0.0637
protein AMBP	4502067	0.92 (0.78-1.08)	0.136	0.82 (0.70-0.97)	0.0008	0.90 (0.76-1.06)	0.0605
protein GNAS isoform XLas	117938759	0.62 (0.24-1.57)	0.1519	0.26 (0.10-0.66)	0.0002	0.42 (0.17-1.08)	0.0125
protein S100-A8	21614544	1.31 (0.79-2.17)	0.1273	0.69 (0.41-1.15)	0.0392	0.53 (0.32-0.87)	0.0004
protocadherin-1 isoform 2	27754773	0.72 (0.35-1.47)	0.1972	0.42 (0.20-0.86)	0.0012	0.58 (0.28-1.19)	0.0375
reticulon-4 receptor-like 2	30425563	0.88 (0.56-1.36)	0.3984	0.52 (0.33-0.80)	<0.0001	0.59 (0.38-0.92)	0.0009
retinoid-inducible serine carboxypeptidase	11055992	0.65 (0.34-1.23)	0.0592	0.37 (0.19-0.70)	<0.0001	0.57 (0.30-1.09)	0.0163
semenogelin-1	4506883	0.16 (0.09-0.30)	<0.0001	0.20 (0.11-0.34)	<0.0001	1.19 (0.66-2.15)	0.4057
semenogelin-2	4506885	0.15 (0.08-0.26)	<0.0001	0.19 (0.11-0.33)	<0.0001	1.32 (0.75-2.35)	0.1659
serotransferrin	4557871	0.79 (0.67-0.93)	<0.0001	0.93 (0.79-1.10)	0.2116	1.18 (1.00-1.40)	0.005
serum albumin	4502027	0.74 (0.67-0.82)	<0.0001	0.79 (0.71-0.87)	<0.0001	1.06 (0.96-1.18)	0.0963
sodium-coupled monocarboxylate transporter 2	157671931	0.42 (0.20-0.90)	0.0058	0.33 (0.15-0.71)	0.0009	0.79 (0.37-1.68)	0.3849
solute carrier family 12 member 1 isoform F	296317278	0.56 (0.27-1.17)	0.0293	0.36 (0.17-0.75)	0.0001	0.63 (0.30-1.32)	0.0812
sortilin-related receptor	4507157	0.77 (0.44-1.35)	0.1948	0.45 (0.26-0.79)	0.0002	0.58 (0.33-1.03)	0.0099
sulfhydryl oxidase 1 isoform a	13325075	0.88 (0.60-1.30)	0.3498	0.61 (0.42-0.91)	0.0005	0.70 (0.47-1.03)	0.0097
syntenin-1 isoform 3	55749523	0.53 (0.22-1.32)	0.0543	0.32 (0.13-0.79)	0.0006	0.60 (0.24-1.47)	0.1096
thrombomodulin	4507483	0.66 (0.33-1.31)	0.0965	0.39 (0.19-0.76)	0.0004	0.58 (0.29-1.15)	0.0318

Protein	GI Accession Number	Mild Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs No Fibrosis)	p-value	Moderate/Severe Fibrosis (vs Mild Fibrosis)	p-value
thyrotropin-releasing hormone-degrading ectoenzyme	7019561	0.62 (0.29-1.32)	0.0782	0.27 (0.13-0.57)	<0.0001	0.44 (0.20-0.93)	0.0031
tripeptidyl-peptidase 1	5729770	0.85 (0.47-1.52)	0.4261	0.53 (0.30-0.96)	0.0027	0.63 (0.35-1.13)	0.0268
tyrosine-protein kinase receptor UFO isoform 2	21536468	0.55 (0.28-1.10)	0.0157	0.35 (0.18-0.71)	<0.0001	0.64 (0.32-1.28)	0.0715
ubiquitin-40S ribosomal protein S27a	4506713	0.78 (0.60-1.00)	0.0056	0.74 (0.57-0.95)	0.0007	0.95 (0.73-1.22)	0.5321
UPF0764 protein C16orf89 isoform 1	307611942	0.34 (0.15-0.77)	0.0004	0.26 (0.11-0.61)	<0.0001	0.77 (0.33-1.80)	0.3876
urokinase-type plasminogen activator isoform 1	4505863	0.76 (0.44-1.33)	0.1711	0.47 (0.27-0.84)	0.0003	0.62 (0.35-1.10)	0.0192
uromodulin	59850812	1.02 (0.85-1.23)	0.731	0.59 (0.49-0.72)	<0.0001	0.58 (0.48-0.70)	<0.0001
vasorin	88702793	0.70 (0.47-1.03)	0.0094	0.44 (0.30-0.65)	<0.0001	0.63 (0.42-0.94)	0.0012
voltage-dependent anion-selective channel protein 1	4507879	0.77 (0.46-1.28)	0.1419	0.42 (0.25-0.70)	<0.0001	0.55 (0.33-0.92)	0.0011
zinc-alpha-2-glycoprotein	4502337	1.20 (0.99-1.45)	0.0087	0.54 (0.45-0.66)	<0.0001	0.45 (0.37-0.55)	<0.0001
zymogen granule protein 16 homolog B	94536866	0.67 (0.33-1.35)	0.1099	0.44 (0.22-0.89)	0.0013	0.66 (0.33-1.32)	0.0937

*p-value of less than 0.003 for a FDR 10%

VITA

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Medical School, MD, University of Kansas, School of Medicine, Kansas City, KS
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08/1993-05/1997

BOARD
CERTIFICATION: USMLE Step 1 – June 2000
USMLE Step 2 – September 2001
USMLE Step 3 – 2003
American Board of Internal Medicine – August 2005
American Board of Nephrology – November 2008

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Illinois State Medical Licensure issued 7/1/2009-Present

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Nephrologist, Locum Tenens. CentraCare Nephrology. St. Cloud, Minnesota.

Nephrologist, Locum Tenens, St. Francis Hospital, Shakopee, Minnesota.

GRANTS: October 2013, Investigator Initiated Study – Questcor Pharmaceuticals (10/2013-9/2016)
"Acthar as Rescue Therapy for Transplant Glomerulopathy in Kidney Transplant Recipients"
(Role: PI)

July 2011, National Kidney Foundation of Illinois (7/2011-6/2014)
"Gene Expression in Kidney Transplant Recipients with Interstitial Fibrosis/Tubular Atrophy"
(Role: PI)

September 2009, NIH K23 DK084121 (9/2009-8/2014)
"Novel Biomarkers in Interstitial Fibrosis/Tubular Atrophy in Kidney Transplants"
(Role: PI)

June 2008, American Society of Transplantation/Roche Clinical Science Fellowship Grant (7/2008-6/2009)
"Proteomic Analysis for Biomarkers of Interstitial Fibrosis/Tubular Atrophy in Kidney Transplant Recipients"
(Role: PI)

May 2006, Amgen Nephrology Fellowship Grant (7/2006-6/2007)
"Proteomic Studies of Hyperfiltration"
(Role: PI)

PROFESSIONAL
MEMBERSHIP: 2005-Present, American Society of Nephrology (ASN)
2005-Present, National Kidney Foundation (NKF)
2006-Present, American Society of Transplantation (AST)
2009-Present, American College of Physicians (ACP)
2009-Present, Central Society for Clinical Research (CSCR)
2010-Present, The Transplantation Society (TTS)
2010-Present, National Kidney Foundation - Illinois Chapter

REVIEWER: Clinical Transplantation
American Journal of Transplantation [ad hoc]
American Journal of Nephrology
Transactions of the Royal Society of Tropical Medicine and Hygiene

TEACHING ACTIVITIES:

1. UIC Endocrine Fellows Lecture (2012-Current) – "Mineral and Bone Disorders in Chronic Kidney Disease"
2. UIC Nephrology Fellows Lectures (2009-Current) - Transplantation Complications, Immunosuppressive Medications, Introduction to Transplant Nephrology
3. UIC MS1 Student Lecture for Human Physiology(Nov 09) – "Body Fluid Compartments"
4. UIC MS2 Student Lecture for Pathophysiology (2010-Current) – "Renal – Introduction and Kidney Function"
5. UIC MS3 Student Lecture for Medicine Clerkship (2009-2012) – "Hypertensive Emergencies"
6. UIC MS3 Student Lecture for Medicine Clerkship (2012-Current) – "Acid-Base Disorders"

PRESENTATIONS:

1. Invited Talk – 4th World Congress on Diabetes and Metabolism – "Proteomic Studies in Renal Transplant Patients"
2. Research Conference – University of Chicago (4/18/13) – "Urine Proteomics in Nephrology"
3. Organ Transplant Support Group (10/7/11) – "Effect of Immunosuppressive Medication on the Kidney"
4. Nursing Conference – University of Illinois at Chicago (6/2/2011) – "Donor and Recipient Evaluation"
5. Medicine Grand Rounds – University of Illinois at Chicago (1/4/2010) – "Diagnosing Chronic Allograft Nephropathy"

PUBLICATIONS:

1. Sreedhar H, Varma VK, Nguyen PL, Davidson B, Akkina S, Guzman G, Setty S, Kajdacsy-Balla A, Walsh MJ. High-definition Fourier Transform Infrared (FT-IR) spectroscopic imaging of human tissue sections towards improving pathology. J Vis Exp. 2015 Jan 21;(95):52332. PubMed PMID: 25650759; PubMed Central PMCID: PMC4395079.

2. Rahman M, Yang W, Akkina S, Alper A, Anderson AH, Appel LJ, He J, Raj D, Schelling J, Strauss L, Teal V, Rader DJ. Serum Lipoproteins and Progression of Chronic Kidney Disease – A Report from the CRIC Study. Clin J Am Soc Nephrol. 2014 Jul;9(7):1190-8.

3. Reid GE, Grim SA, Layden JE, Akkina S, Tang I, Campara M, Clark NM. The Use of Fosfomycin to Treat Urinary Tract Infections in Kidney Transplant Recipients. Transplantation. 2013;96(3):e12-4.

4. Porter A, Gilmartin C, Srisakul U, Arruda J, Akkina S. Prevalence of 25-OH Vitamin D Deficiency in a Population of Hemodialysis Patients and Efficacy of an Oral Ergocalciferol Supplementation Regimen. Am J Nephrol. 2013;37(6):568-74.

5. Oberholzer J, Giulianotti P, Danielson KK, Spaggiari M, Bejarano-Pineda L, Bianco F, Tzvetanov I, Ayloo S, Jeon H, Garcia-Roca R, Thielke J, Tang I, Akkina S, Becker B, Kinzer K, Patel A, Benedetti E. Minimally invasive robotic kidney transplantation for obese patients previously denied access to transplantation. Am J Transplant. 2013;13(3):721-8.

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11. Akkina SK, Muster H, Steffens E, Kim SJ, Kasiske BL, Israni AK. Donor Exchange Programs in Kidney Transplantation: Rationale and Operational Details From the North Central Donor Exchange Cooperative. Am J Kidney Dis. 2010 Aug. PMID: 20692751

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13. Sebasky, M., Kukla, A., Leister, E., Guo, H., Akkina, SK, El-Shahawy, Y., Matas, AJ, Ibrahim, HN. Appraisal of GFR-estimating equations following kidney donation. Am J Kidney Dis. 2009 Jun. 53(6):1050-8. PMID 19394733.

14. Ibrahim HN, Akkina SK, Leister E, Gillingham K, Cordner G, Guo H, Bailey R, Rogers T, Matas AJ. Pregnancy outcomes after kidney donation. Am J Transplant. 2009 Apr;9(4):825-34. PMID: 19353771.

15. Akkina SK, Zhang Y, Nelsestuen GL, Oetting WS, Ibrahlm HN. Temporal stability of the urinary proteome after kidney transplant: more sensitive than protein composition? J Proteome Res. 2009 Jan;8(1):94-103. PMID: 19012427.

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ABSTRACTS:

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2. Jain-Arwindekar D, Belur RC, Chon WJ, Desai AS, Tang IYS, Josephson, MA, Akkina SK. Impact of Maintenance Steroids versus Rapid Steroid Withdrawal in African-American Kidney Transplant Recipients: Comparison of Two Centers. J Am S Nephrol. 2012. 22:855A [Poster].

3. Akkina SK, Mahmud MK, Tang IYS. Screening for Adequate GFR in Obese Potential Kidney Donors. J Am S Nephrol. 2012. 22:363A [Poster].

4. Walczak DA, Akkina SK, Walczak D, Moore J, Marquez G, Kemerley P, Ahlstrom R, Tzvetanov I, Oberholzer J, Benedetti E. The Age Factor: A Retrospective Analysis of Kidney Transplant in Elderly Recipients. Am J Transplant. 2012 May. 12(s3):102 [Oral]

5. Reid G, Grim S, Layden J, Akkina SK, Tang IYS, Adams W, Campara M, Janda W, Clark N. The Use of Fosfomycin (FOS) To Treat Urinary Tract Infections (UTIs) in Renal Transplant Recipients (RTRs). Am J Transplant. 2012 May. 12(s3):212 [Poster]

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10. Porter AC, Aggarwal N, Tang IYS, Akkina SK. Comparison of Two Nuclear Scan Tracer Methods for Accurate Assessment of Kidney Donor Glomerular Filtration Rate. J Am S Nephrol. 2011. 21:333A [Poster]

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33. Tan, L.T., Akkina, S., Schneider, E., and Smith, C.L (2007) High Prevalence of 25-Hydroxyvitamin D Deficiency in Hemodialysis Patients. J Am Soc Nephrol 18:530A. [Poster]

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