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Award Number: W81XWH-10-1-0433

TITLE: Biomarkers of Renal Tumor Burden and Progression in TSC

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REPORT DATE: September 2013

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2013	Final	1 September 2010 - 31 August 2013

4. TITLE AND SUBTITLE

Biomarkers of Renal Tumor Burden and Progression in TSC

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0433

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Massachusetts General Hospital
Boston, MA 02114-2554

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Renal lesions in TSC can cause significant morbidity and mortality. Most solid renal lesions of TSC are angiomyolipoma (AML), but some are malignant. Moreover, hemorrhagic AMLs can be life threatening. Hypothesizing that renal tumor growth is associated with measurable changes in urine composition, we designed a biomarker discovery project to identify factors that reflect renal tumor burden. We proposed to (A) monitor progression of renal disease with prospective and retrospective review of a large population of TSC patients and to (B) measure soluble factors in urine from patients with TSC in search of candidate markers of renal tumor burden. We noted renal lesions in 85% of our enrolled patients. More common that previously reported, cysts occurred in n 75% of patients; masses in 70%. Patients with TSC2 gene mutations (versus TSC1) have substantially more renal lesions. TSC2 is overrepresented among patients requiring biopsy or embolization of renal lesions. The biomarker discovery of this project was disappointing. More power is needed to address clinical variables that impact urine composition. Assessment of renal function revealed CKD at substantially higher frequencies in TSC than in the general population. TSC patients have approximately 15 times more CKD at 40-60 years of age, and those with TSC2 gene mutations display as much as 30-fold increased incidence of CKD compared to the general population. TSC genotype therefore has significant prognostic implications. Standard of care should include routine genotyping and regular creatinine measurement in all TSC patients to help guide clinical management and lifelong surveillance for TSC associated renal complications.

15. SUBJECT TERMS
renal angiomyolipoma; urine biomarkers; GFR; CKD

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION:

Renal lesions occur commonly in people with TSC and can cause significant morbidity and mortality [1]. Although most solid renal lesions of TSC are benign angiomyolipoma (AML), some are in fact cancerous. Moreover, rapidly growing AMLs can be life threatening when abnormal blood vessels rupture [2]. Based on the hypothesis that renal tumor growth is associated with measurable changes in urine composition and on the knowledge that angiogenesis is essential for tumor expansion [3, 4], we have predicted that factors associated with angiogenesis and with renal injury will increase during periods of TSC-associated renal tumor growth. We are testing this candidate driven approach to identify factors in urine or serum that reflect renal tumor burden and whose concentrations change as tumors grow. This project can be described in two aims. (A) Monitor the progression of TSC renal disease by combining prospective data collection with retrospective chart review of a large population of TSC patients with respect to gender, age, patient size, TSC genotype, renal lesions (e.g. lesion number, appearance and growth rates) and renal function parameters (e.g. blood pressure, serum chemistries, urinalysis and urine chemistries). (B) Measure soluble growth factors, angiogenesis factors and renal injury molecules in urine and serum samples from patients with TSC and evaluate these candidates as surrogate markers of renal tumor burden and growth.

BODY:

Building a biorepository:

The Statement of Work (SOW) was divided into four blocks of 6 months each, denoted here as "quarters". Goals met during the first quarter of the project, from 09/01/2011 to 03/01/2012, included initiation of the study with hiring and training of personnel, purchase of start-up equipment and education of support staff. Patient enrollment began smoothly in October 2011 so that 36 patients were enrolled and 41 urine and blood samples were collected, de-identified and processed for secure storage. Goals met during the second quarter of the project, from 03/01/2012 to 09/01/2012 included ongoing patient enrollment, sample collection and database expansion. During that period an additional 35 patients were enrolled, bringing the patient total to 71, and 36 urine and blood samples were collected, de-identified and processed for secure storage, bring the sample total to 77.

At the first annual review, the total patient enrollment (N=71) was lower than anticipated (target 75-150). Three previously unappreciated factors were noted to contribute to this lag, as follows. (1) Not all cognitively impaired TSC patients are accompanied by their legal guardians. These patients are therefore not approached for the study in absence of a guardian. (2) TSC patients under stress that are seen urgently for acute issues rather than routine annual follow up have not been approached regarding the study. (3) Non-TSC patients with acute issues are periodically given appointment slots in TSC clinic, thus undermining our initial estimates that were based on total patient visits per TSC clinic per month rather than total TSC patient visits per TSC clinic per month. As a result of these observations, we revised our enrollment and milestone projections for the second year of the project and updated the SOW accordingly.

During the 3rd and 4th quarters of the project from 09/01/2012 to 03/01/2013 and from 03/01/2013 to 09/30/2013, respectively, patient enrollment and sample collection were ongoing, bringing our repository to a total of 121 samples from 100 patients by the end of the 2 year

project period. The total number of patients enrolled fell short of expectation for reasons obvious in retrospect. During the first year of the project, the bulk of the newly enrolled patients were new to the project, but not new to our TSC center which allowed for streamlined enrollment of patients who already "knew the system". During the second year of the project period, the majority of new patients available for recruitment were also new to our TSC center, and many indeed new to the TSC diagnosis itself. This cohort of potential subjects is less readily approached in the clinical setting where they have many novel questions, concerns and trepidations. These individuals will be more easily approached and enrolled upon return visits. Despite falling short of anticipated patient enrollment, we were nonetheless able to reach our projected target for sample collection, and can use this experience for better projections in the future.

Demographics of the 100 enrolled patients were as follows:

- Gender: 59 female; 41 male
- Average age at enrollment was 23 years, ranging from 2 to 66.
- Genotyping of TSC gene mutations was performed on 89 of the patients, of whom 25% had mutations in TSC1, 60% had mutations in TSC2 and 15% had no mutation identified.
- Fewer than 15% of patients had no renal findings to speak of.
- Approximately 75% of patients had renal cysts. Two of these patients had PKD in addition to TSC due to contiguous gene syndrome involving TSC2 and PKD1.
- Approximately 67% of patients had renal masses that were primarily AMLs. Biopsies of lipid poor renal tumors were performed on 13 patients, and RCC was diagnosed in one instance. Embolizations of large renal AMLs were performed on 14 patients.
- Of 23 patients with TSC1 gene mutations, 65% had cysts and 26% had masses
- Of 53 patients with TSC2 gene mutations, 89% had cysts and 79% had masses
- Of 14 patients requiring embolization of renal AMLs, 12 had TSC2 gene mutations, 2 had no mutation identified, and one did not have genotyping performed.
- Of 13 patients requiring biopsy of suspicious renal lesions, 9 had TSC2 gene mutations, one had no mutation identified, and 2 did not have genotyping performed.

Biomarker screening:

Since the last reporting period, biomarker screening was initiated. The total number of screened samples (N=30) was determined by budget. Urine samples from 30 patients with TSC were selected with the intention of spanning the spectrum of possible renal phenotypes. This included patients with normal renal imaging (N=4), patients with minimal cystic involvement (N=2), patients with small (N=4), medium (N=9) and large renal AMLs (N=9) as well as patients with TSC plus CKD (N=2). The patients in this group included 11 males and 19 females, ranging in age from 4 to 47 years (mean 19). Three of these patients had disease associated mutations in TSC1 genes, 26 in TSC2 genes and one patient had no mutation identified. The genotype skewing is a result of the increased tendency for renal involvement in the setting of TSC2 gene mutations.

The 30 urine samples were tested on two RayBiotech, Inc. (Norcross, GA) glass format protein arrays (Human L-507 array and Human AKI array). The nearly 530 human protein analytes

covered by these arrays are listed in Appendix 1. The raw data from these screening assays were processed in a variety of ways; normalizing to technical controls and to biological controls including urine creatinine, total urine protein as well as urine albumin.

There was no particular analyte or analyte subset that stood out above the rest upon graphical analysis of the data. For statistical analyses, the samples were initially divided into 3 groups based on phenotype: the nil group (N=6), the low involvement group (N=13) and the high involvement group (N=9). The two samples from patients with PKD were excluded at this point. In consultation with our biostatistician, a number of statistical tests were applied in attempt to discover significant differences between the groups of any one or two analytes without success. The dataset was impacted by relatively low power in the setting of a relatively large number of analytes, leading to a relatively high false discovery rate. Power was not adequately improved when patient samples were clustered in two rather than three groups. There was similarly no success when statistical review was applied exclusively to analytes within the AKI panel or restricted to the subset of analytes involved in angiogenesis.

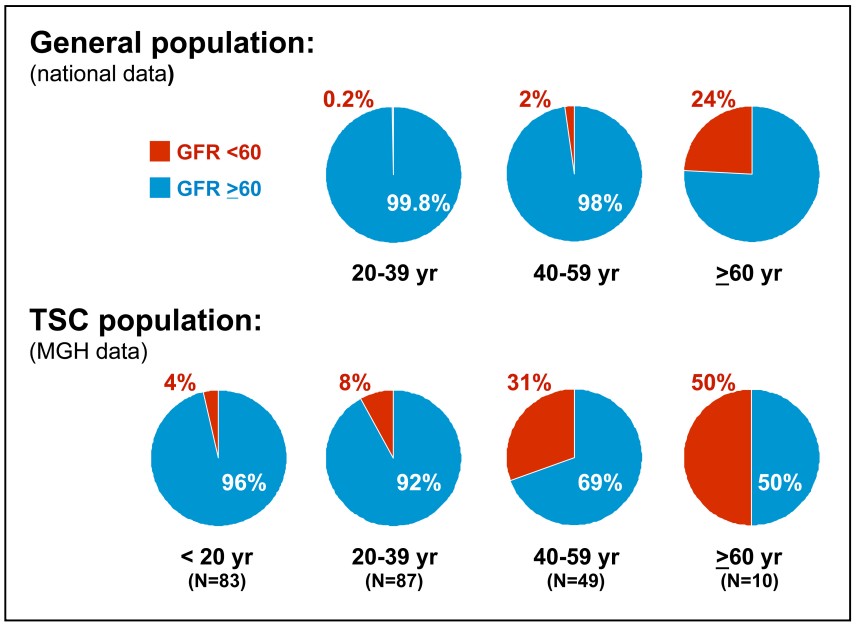
In absence of statistically significant biomarker candidates, a few analytes were selected for further analysis based on suggestive p values. For the analytes, FGF basic, CCL2 and TIMP-1, ELISAs were tested first on select samples within the original 30-sample panel. FGF was abandoned when high and low samples from the array analysis did not behave similarly in the ELISA. When tested on 80 samples available from 72 patients, the dynamic range of the CCL2 ELISA was unacceptably limited compared to the standard curve. This limitation restricts its ability to discriminate between samples from TSC patients with normal (or nearly normal) and abnormal kidneys. In contrast, the TIMP-1 ELISA displayed a wider range of data points. Of the 8 patients with two serial urine samples each, there was remarkably tight correlation of TIMP-1-to-creatinine ratios among each pair with the exception of one that jumped nearly 20-fold in 7 months without clear clinical correlate. However, there was no discernable association of urine TIMP-1 with any renal phenotype, nor with age, gender or use of antiepileptic drugs. Whether additional analysis of the current data will yield additional candidates is not yet clear. In all likelihood, the search for novel biomarkers needs to include not only many more patient samples, but also the analysis of multiple analytes at the same time. While this initial pilot study has not identified a suggestive candidate molecule, it has nonetheless set in motion a mechanism for collecting, storing and annotating patient samples that will hopefully be fruitful upon expansion.

Chronic kidney disease in TSC:

During chart review of the renal phenotypes in our TSC patients supported by this funding mechanism, we became aware of the inadequate prognostic data that exists for predicting renal insufficiency in this population. This realization prompted the assessment of renal function in our patient cohort, with comparison to the non-TSC general population captured by the U.S. Renal Data System, USRDS 2012 Annual Data Report: NIH, NIDDK.

We used serum creatinine measurements to estimate glomerular filtration rates and hence renal function of patients with TSC. The modified Schwartz equation (eGFR = 0.413 x height [in cm] / cre [mg/dL]) was used for pediatric patients and CKD-EPI for adults (eGFR=141 $x\min(cre/\kappa,1)^{\alpha}$ $x\max(cre/\kappa,1)^{-1.209}$ $x0.993^{Age}$ x1.018 [if female] x1.159 [if black]). Estimated GFR was converted

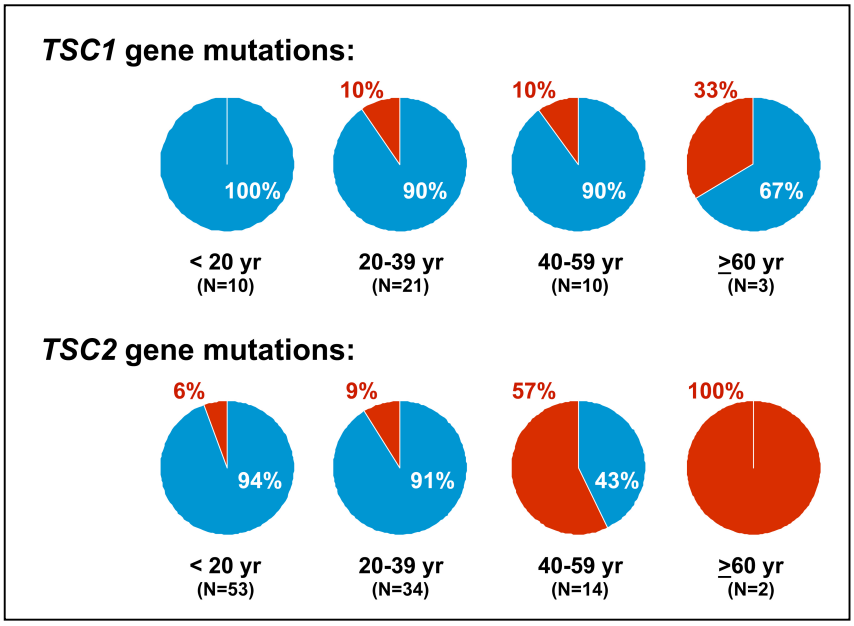
to CKD stages 1 through 5 based on standard cut-offs of 90, 60, 30, and 15 ml/min/1.73m^2 and eGFR > or < 60 was used to delineate normal versus impaired renal function in a binary manner.



The prevalence of CKD increases with age. In the 20-39 yr age group of the US general population (top row), GFR <60 (CKD3-5) is uncommon (0.2%). The prevalence of CKD increases 10-fold in 40-59 yr olds (2%), and then 10-fold again in the >60 yr group (24%).

In contrast, our retrospective review suggested that the prevalence of CKD is alarmingly high in the TSC population (2nd row). Four percent of children with TSC have GFR <60 (95% CI 0.8-10.2%), without national norms for comparison. CKD 3-5 occurs 40 time more often in young adults with TSC (8%; 95% CI 3.3-15.9%) than the general population, 14 times more in the middle aged group (31%; 95% CI 18.3-45.4%) and twice as frequently >60 yr (50%; 95% CI 18.7-31.3%).

When renal function is similarly evaluated in TSC patients based on their TSC gene mutations, we found a tendency for greater renal decline in the presence of *TSC2* versus *TSC1* gene mutations, with significantly more CKD in the 40-59 yr old group I particular (p=0.02 by Fisher exact test). The higher prevalence of *TSC2*-associated renal failure presumably reflects the greater number and larger size of renal lesions that are associated with *TSC2* versus *TSC1* gene mutations.



Drilling down to try to identify specific risk factors for CKD, we compared renal function in TSC patients with different renal phenotypes. We found no significant increase in CKD in those TSC patients with cysts versus those with normal renal anatomy, excluding patients with PKD,

and similarly no significant increase in CKD in patients with "undisturbed" AMLs versus those with cysts or normal renal anatomy. Biopsy of AMLs had no effect on eGFR.

Patients who required embolization had more CKD than those with smaller AMLs ($p<0.04$ by Fisher exact test) and surgical intervention further increased CKD compared to embolization ($p<0.03$). This sample group showed similar impact of partial and total nephrectomy on GFR.

From this review (presented at the 2013 annual International Research Conference on TSC) we concluded that renal failure is an under-recognized and potentially severe manifestation of TSC. CKD was seen in our single center TSC population at rates ranging from 2 to 40 times greater than the general population, depending on the age group in question. The greatest increase in CKD was apparent in TSC patients aged 20-60 years.

Predictably, patients with *TSC2* gene mutations that impart an increased frequency and severity of renal involvement also had more CKD than those with *TSC1* mutations. However, the mere presence of renal lesions was not closely associated with CKD in this dataset. The incidence of CKD in TSC patients with AMLs and cysts is not substantially greater than TSC patients with normal kidneys or cysts alone, as long as there is not also polycystic kidney disease (PKD). Similarly, biopsy of renal masses has no overt impact on the risk of CKD.

Patients requiring embolization had more CKD that those who did not, and patients undergoing surgical procedures had more still. While embolization and surgery may themselves increase the risk of renal failure, it is likely that patients requiring such interventions are at greater risk to begin with due to greater renal involvement.

This retrospective study was limited by an over-representation of patients with substantial renal involvement. This bias likely overestimated the frequency and severity of renal insufficiency in the TSC population. Until prospective studies of renal function in all TSC patients better delineate the risks of renal failure in the TSC population, we now recommend that routine surveillance include creatinine measurements in all TSC patients regardless of renal imaging results, with early referral to renal specialists when indicated

KEY RESEARCH ACCOMPLISHMENTS:

- The most significant accomplishment to date is the initial collection of a relatively large number of samples from a carefully monitored population of people with TSC. This resource can potentially grow into a "tissue bank" for supplementary follow up studies.
- Radiologic review of patients in this cohort demonstrates more cystic lesions than previously appreciated and confirms nonetheless that patients with TSC2 gene mutations have a greater burden of renal lesions than those with TSC1 gene mutations.
- Retrospective review of renal function in the TSC patient cohort has demonstrated that there is substantially more chronic kidney disease in TSC compared to the generally population. This warrants prospective evaluation.

REPORTABLE OUTCOMES:

- The existence of this DoD award enabled application for additional funds to supplement this project. As a result, the project was awarded a $10K credit at RayBiotech, Inc., a commercial company that produces reagents, kits and large scale protein arrays designed for biomarker discovery and validation studies. This award was reported to DoD in last year's report.
- The retrospective assessment of TSC associated CKD reported herein was presented at the 2013 annual International Research Conference on TSC. This will likely form the basis for a prospective study of CKD in TSC.

CONCLUSION:

In the course of building our annotated TSC biorepository we have noted that renal lesions are seen in approximately 85% of patients with TSC in our cohort ranging from 2 to 66 years of age. Cysts are more common that previously reported, present in 75% of all TSC patients. Masses are present in just under 70%, albeit not adjusted for age. Of 23 patients with TSC1 gene mutations, 65% had cysts and 26% had masses whereas, of 53 patients with TSC2 gene mutations, 89% had cysts and 79% had masses. Remarkably, of the patients within this cohort requiring biopsy of suspicious renal lesions and/or embolization of large renal AMLs, the vast majority had mutations of TSC2 genes. The remainder had either no mutation identified or were not tested for genotype.

The biomarker discovery portion of this project was not successful. Results indicate that substantially more power will be needed for this kind of unbiased approach to work. Nonetheless, our experience in this project has helped build a streamlined system for collecting, storing and annotating patient samples that will hopefully be fruitful upon expansion.

Assessment of renal function and prevalence of CKD within our TSC population revealed that CKD occurs at substantially higher frequencies than in the general population. TSC patients have approximately 15 times more CKD at age 40 to 60 years of age compared to the general population, and those with TSC2 gene mutations display as much as 30-fold increased incidence of GFR<60 ml/min/1.73m^2.

Taken together, our observations indicate that TSC genotype has significant prognostic implications. We recommend that standard of care in TSC include routine genotyping of all patients and regular measurement of serum creatinine to help guide the clinical management and lifelong surveillance for TSC associated renal complications.

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APPENDIX:
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17D, IL-17E, IL-17F, IL-17R, IL-17RC, IL-17RD, IL-18 BPa, IL-18 R alpha (IL-1 R5), IL-18 R beta (AcPL), IL-19, IL-2, IL-2 R alpha, IL-2 R beta (CD122), IL-2 R gamma, IL-20, IL-20 R alpha, IL-20 R beta, IL-21, IL-21 R, IL-22, IL-22 BP, IL-22 R, IL-23, IL-23 R, IL-24, IL-26, IL-27, IL-28A, IL-29, IL-3, IL-3 R alpha, IL-31, IL-31 RA, IL-4, IL-4 R, IL-5, IL-5 R alpha, IL-6, IL-6 R, IL-7, IL-7 R alpha, IL-8, IL-9, Inhibin A, Inhibin B, Insulin, Insulin R, Insulysin (IDE), IP-10, I-TAC (CXCL11), KGF-2, Kininostatin (Kininogen), Kremen-1, Kremen-2, Latent TGF beta bp1, LBP, Lck, LECT2, Lefty - A, Leptin (OB), Leptin R, LFA-1 alpha, LIF, LIF R alpha, Light, Lipocalin-1, Lipocalin-2, LRP-1, LRP-6, L-Selectin (CD62L), Lymphotactin (XCL1), Lymphotoxin beta (TNFSF3), Lymphotoxin beta R (TNFRSF3), MAC-1, MCP-1, MCP-2, MCP-3, MCP-4 (CCL13), M-CSF, M-CSF R, MDC, MFG-E8, MFRP, MIF, MIG, MIP 2, MIP-1 alpha, MIP-1 beta, MIP-1 delta, MIP-3 alpha, MIP-3 beta, MMP-1, MMP-10, MMP-11 (Stromelysin-3), MMP-12, MMP-13, MMP-14, MMP-15, MMP-16 (MT3-MMP), MMP-19, MMP-2, MMP-20, MMP-24 (MT5-MMP), MMP-25 (MT6-MMP), MMP-3, MMP-7, MMP-8, MMP-9, MSP alpha chain, Musk, NAP-2, NCAM-1 (CD56), Neuregulin, Neuritin, NeuroD1, Neuropilin-2, Neurturin, NGF R, NOV (CCN3), NRG1 Isoform GGF2, NRG2, NRG3, NT-3, NT-4, Orexin A, Orexin B, OSM, Osteoactivin (GPNMB), Osteocrin, Osteoprotegerin (Osteoprotegerin), OX40 Ligand (TNFSF4), PARC (CCL18), PD-ECGF, PDGF R alpha, PDGF R beta, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-C, PDGF-D, PECAM-1 (CD31), Pentraxin3 (TSG-14), Persephin, PF4 (CXCL4), PLGF, PLUNC, Pref-1, Progranulin, Prolactin, P-selectin, RAGE, RANK (TNFRSF11A), RANTES, RELM beta, RELT (TNFRSF19L), ROBO4, S100 A8/A9, S100A10, SAA, SCF, SCF R (CD117), SDF-1 (CXCL12), sFRP-1, sFRP-3, sFRP-4, sgp130, SIGIRR, Siglec-5 (CD170), Siglec-9, SLPI, Smad1, Smad4, Smad5, Smad7, Smad8, SMDF (NRG1 Isoform), Soggy-1, Sonic Hedgehog (ShhN-terminal), SPARC, Spinesin, TACI (TNFRSF13B), Tarc, TCCR (WSX-1), TECK (CCL25), TFPI, TGF alpha, TGF beta 1, TGF beta 2, TGF beta 3, TGF beta 5, TGF beta RI (ALK-5), TGF beta RII, TGF beta RIIb, TGF beta RIII, Thrombopoietin (TPO), Thrombospondin (TSP), Thrombospondin-1, Thrombospondin-2, Thrombospondin-4, Thymopoietin, Tie-1, Tie-2, TIMP-1, TIMP-2, TIMP-3, TIMP-4, TL1A (TNFSF15), TLR1, TLR2, TLR3, TLR4, TMEFF1 (Tomoregulin-1), TMEFF2, TNF RI (TNFRSF1A), TNF RII (TNFRSF1B), TNF alpha, TNF beta, TNFSF14, TRADD, TRAIL (TNFSF10), TRAIL R1 (DR4, TNFRSF10A), TRAIL R2 (DR5, TNFRSF10B), TRAIL R3 (TNFRSF10C), TRAIL R4 (TNFRSF10D), TRANCE, TREM-1, TROY (TNFRSF19), TSG-6, TSLP R, TWEAK (TNFSF12), TWEAK R (TNFRSF12), Ubiquitin+1, uPA, uPAR, Vasorin, VCAM-1 (CD106), VE-Cadherin, VEGF-A, VEGFR2 (KDR), VEGFR3, VEGF-B, VEGF-C, VEGF-D, VEGI (TNFSF15), WIF-1, WISP-1 (CCN4), XEDAR

RayBio® G-Series Human Acute Kidney Injury Antibody Array 1 Kit.
Detects 20 Human Cytokines.
KIM-1, Albumin (ALB), Osteopontin (Osteopontin), Trefoil Factor 3 (TFF3), B2M, Clusterin (CLU), CXCL16, Osteoactivin, Liver-type fatty acid binding protein (L-FABP), MCP-1, sTNFRI, Calbindin (CALB1), Interferon gamma-induced protein 10 (IP-10), Cystatin C, HGF, MIF, NGAL, TIMP-1, VCAM-1, VEGF-A