



Novel Renal Biomarkers of Acute Kidney Injury and FDA Qualifications

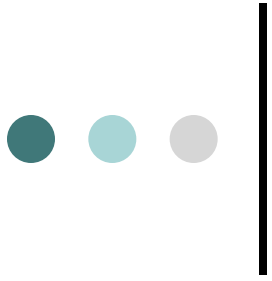
CMOD 2011

Melanie J Blank, MD



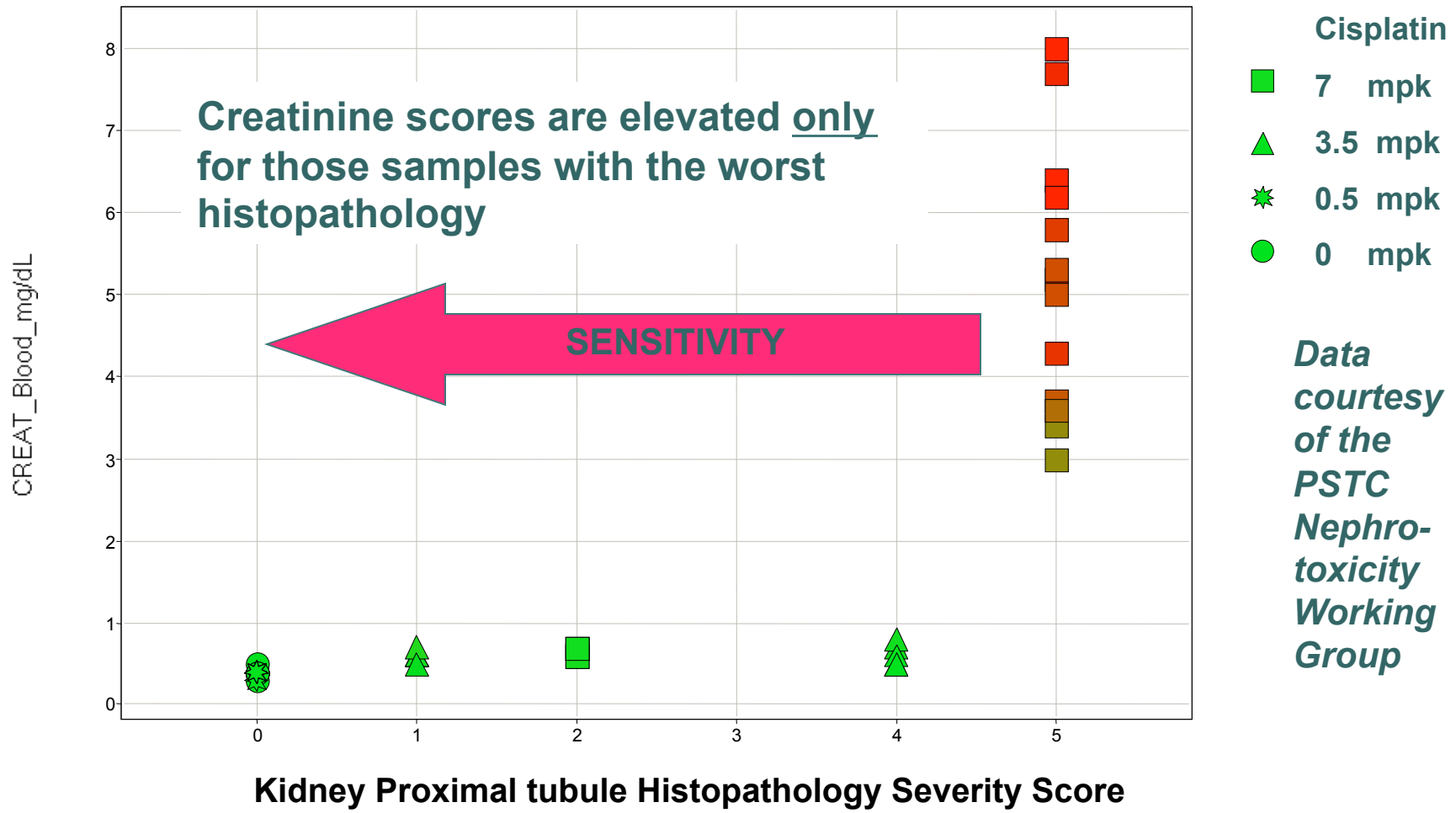
OUTLINE

- General understanding of how biomarkers of kidney injury can facilitate drug development
- 2 examples of nonclinical renal biomarker submissions that in partnership with FDA and EMA resulted in qualification
 - PSTC/ C-PATH
 - ILSI-HESI
- Evolving standards for qualification
- Show a proposal by PSTC/FNIH for how certain novel clinical biomarkers of kidney injury would be used in clinical trials



Why we aren't satisfied with serum Creatinine as a marker of acute kidney injury

Creatinine is NOT a sensitive biomarker of acute kidney injury





Novel biomarkers of AKI aren't necessarily that novel

- Research has been haphazard over last decades
- Lack of collaboration
- Lack of good truth standard since creatinine elevation can result from other things other than acute kidney injury (decreased secretion, hemodynamic factors, or trauma).



Ideal Qualities of Biomarkers of Injury

- Translatable
- Urinary or Serum
- Highly sensitive and highly specific for early injury
- Linger for some period of time after injury so that the elevation is not easy to overlook
- Levels change during repair
- Biomarker can be preserved in vitro for later measurement
- Accurate assay

Emphasis has been on biomarker discovery. There are dozens of discovered renal biomarkers – few have been studied to see if they possess most of these qualities.

- ● ● | Potential Contexts of Use for Novel Biomarkers of Acute Kidney (Organ) Injury
- Safety in early clinical trials
 - To allow drugs with preclinical renal toxicity signals to be studied safety in the clinic (since BUN and Cr only detect Δ s in function)
- Biological Process biomarkers
 - To monitor the activity of a drug (measuring a pharmacodynamic action such as INR)



Other Potential Contexts of Use for Novel Biomarkers

- Proof of concept endpoints
- Establishing NOAEL
- Trial enrichment
- Assist in dose finding for drugs intended to prevent AKI
- Understand location and mechanism of injury in patients
- To serve as surrogate endpoints for clinically meaningful renal efficacy endpoints (? How realistic)



Public-Private Partnership Examples

PSTC (Predictive Safety Testing Consortium) and FDA and EMA:

TRANSLATABLE URINARY BIOMARKERS

- Kim-1
- Clusterin
- Trefoil Factor 3
- Albumin

Tubular injury
markers

- Cystatin C
- Beta 2 Microglobulin
- Protein

Glomerular injury
markers



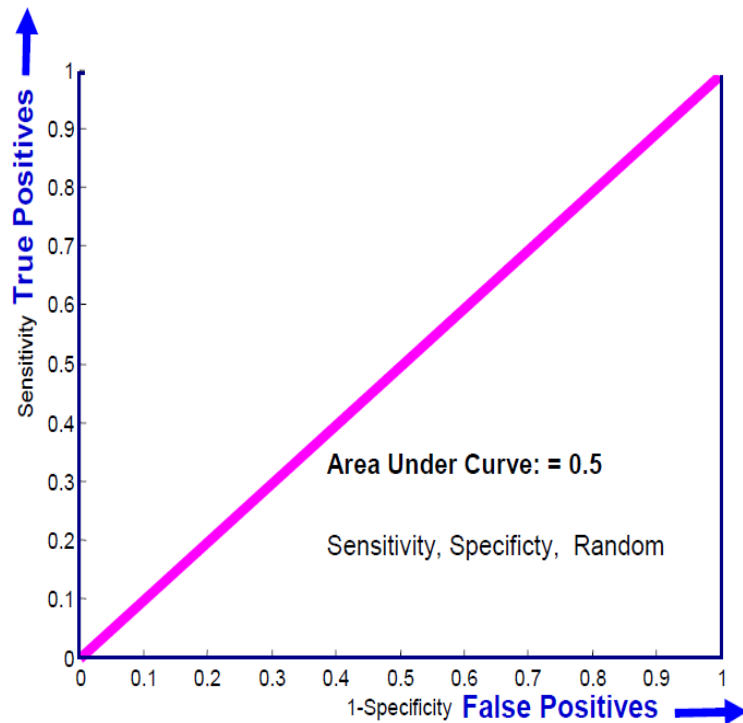
Methodology used for Preclinical Biomarker Studies

- Expose rats to different doses of known nephrotoxicants that injure specific portions of the nephron
- Assay urinary biomarkers and histopathology (truth standard) at a prespecified timepoint after exposure
- Analyze ability of biomarker to detect presence and absence of toxicity through use of ROC curves

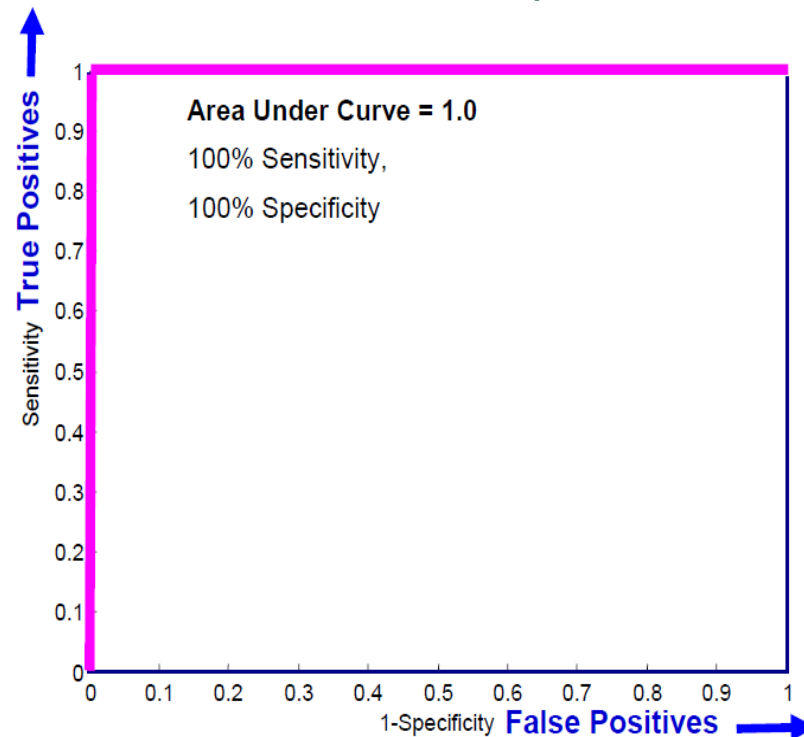


ROC analysis displays biomarker performance across all possible thresholds

Random result



Perfect biomarker pattern

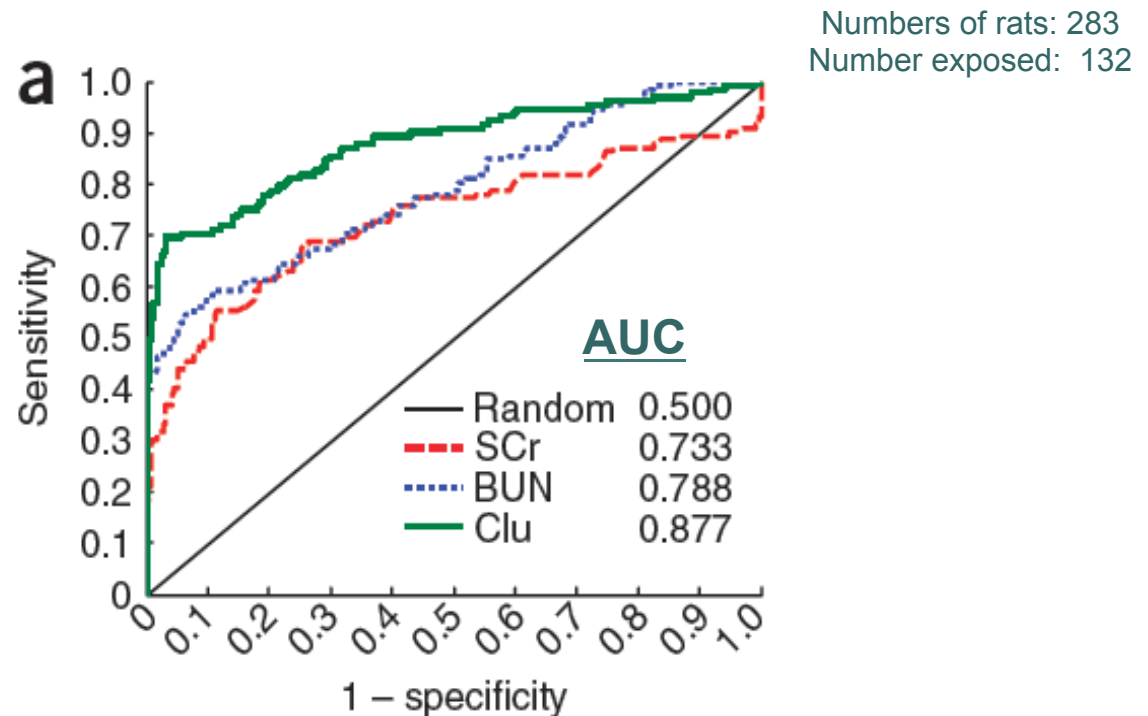


ROC = Receiver operating characteristic

Courtesy of Pat Harlow, PhD, DCRP

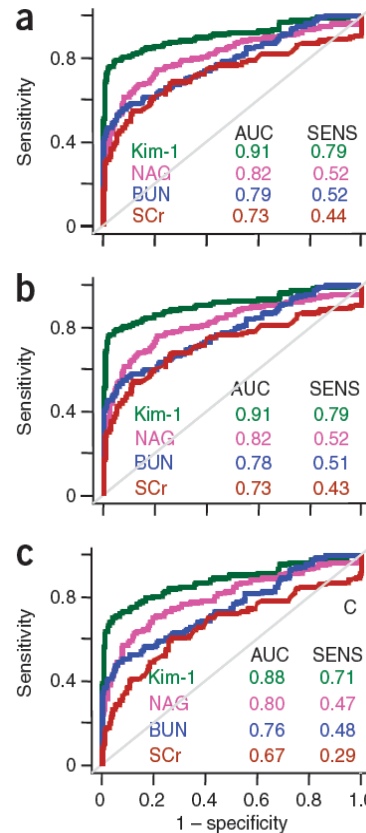


ROC curves for tubular injury biomarker urinary clusterin compared to BUN and Cr



ROC curves and AUC and sensitivity graphs for urinary Kim-1 compared to BUN and Cr in Tubular Injury

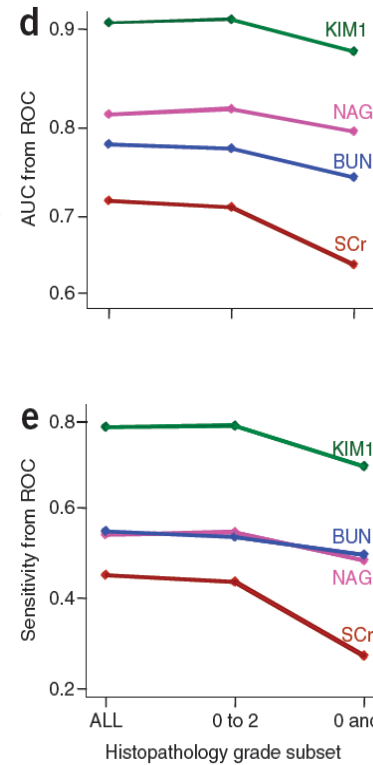
All histopathology grades



Histopathology grade 0 to 1, 2



Histopathology grade 0 to 1



Numbers of rats: 283

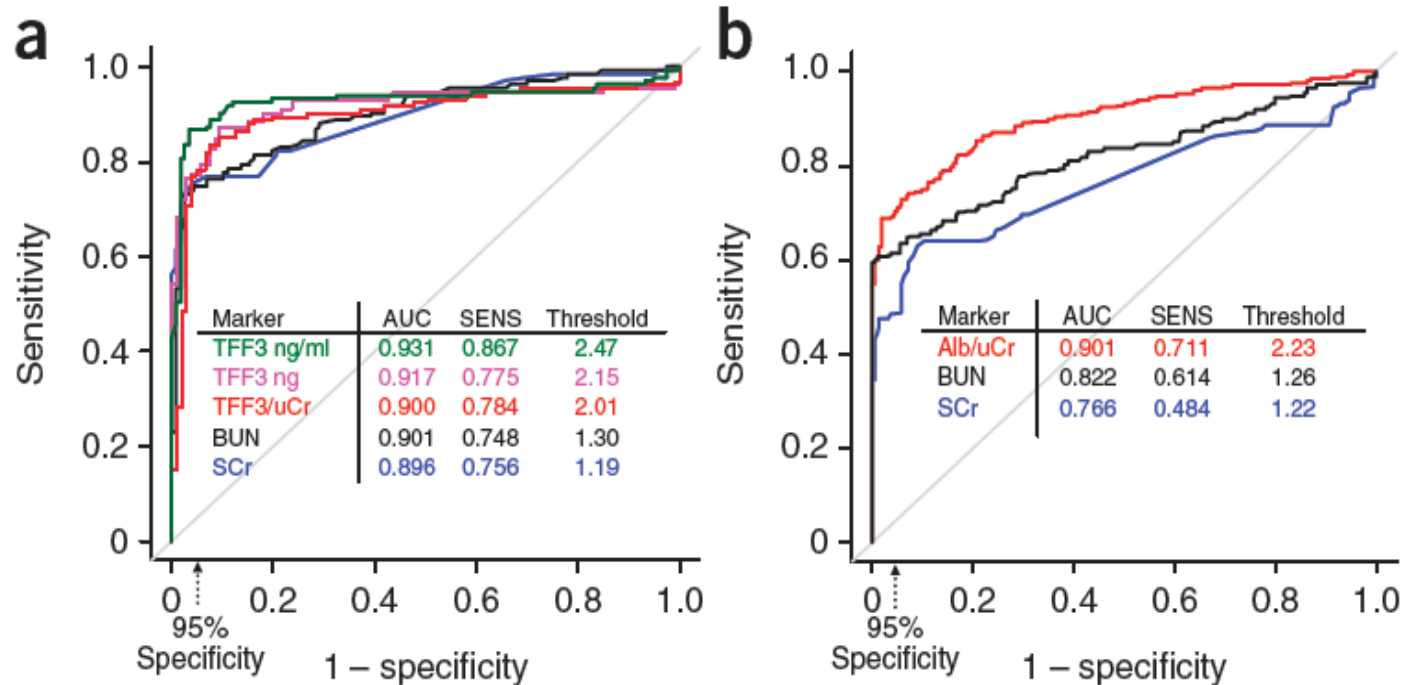
Numbers exposed:

All: 132

0-2: 120

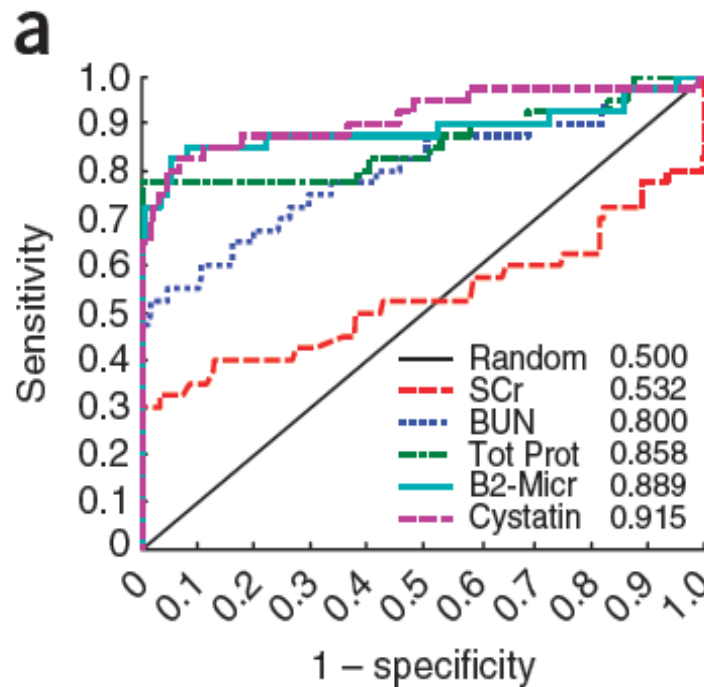
0-1: 94

ROC curves for urinary TFF3 and urinary Albumin compared to BUN and Cr in tubular injury – excluding animals with grade 0 histopathology

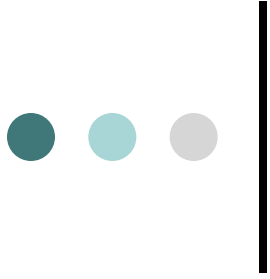




ROC curves for glomerular injury biomarkers: Total urinary protein, urinary B2-microglobulin, urinary Cystatin C, BUN and Cr



Number of rats: 331
Numbers exposed to nephrotoxicants: 40

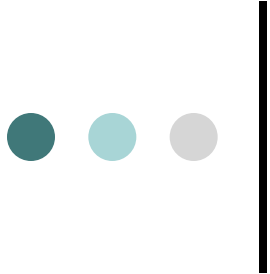


Qualification- excerpt from Dr. Woodcock's letter to PSTC 4/14/08 (from PSTC website)

Recommended application context for the voluntary use of these urinary biomarkers using the test parameters submitted:

KIM-1, Albumin, Clusterin and Trefoil Factor-3 can be included as biomarkers of drug-induced acute kidney tubular alterations in Good Laboratory Practice (GLP) rat studies used to support clinical trials.

Total Protein, β 2 Microglobulin and Cystatin C can be included as biomarkers of acute drug-induced glomerular alterations/damage and/or impairment of kidney tubular re-absorption in GLP rat studies used to support clinical trials.



Addressing Clinical Uses: excerpt from Janet Woodcock's letter to PSTC 4/14/08 (from PSTC website)

Clinical use of these urinary biomarkers:

While considerable human data exist for some of these novel biomarkers, they are not currently qualified for routine monitoring of drug-induced nephrotoxicity in the clinical setting. In cases where additional evaluation of drug effect on the kidney is deemed useful, the sponsor and FDA's clinical review division will decide on a case by case basis how best to implement the use of these biomarkers in a clinical development program.



ILSI-HESI

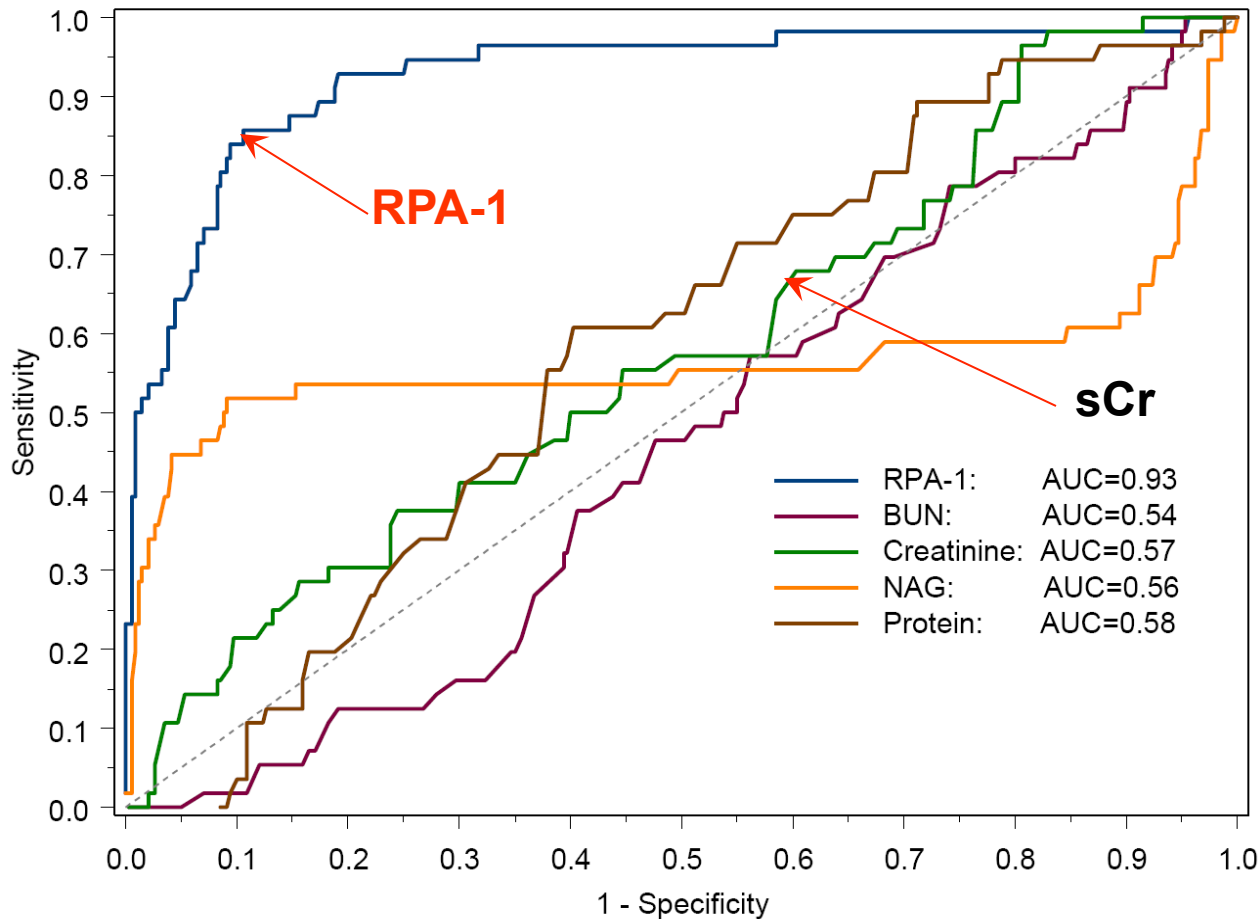
○ ILSI-HESI, FDA and EMA:

URINARY BIOMARKERS

- Clusterin: tubular injury marker
- Renal Papillary Antigen-1: collecting duct injury marker
- Alpha GST: tubular and collecting duct injury marker



ROC analysis: CD degeneration or necrosis RPA-1 versus BUN, sCr, NAG, and protein



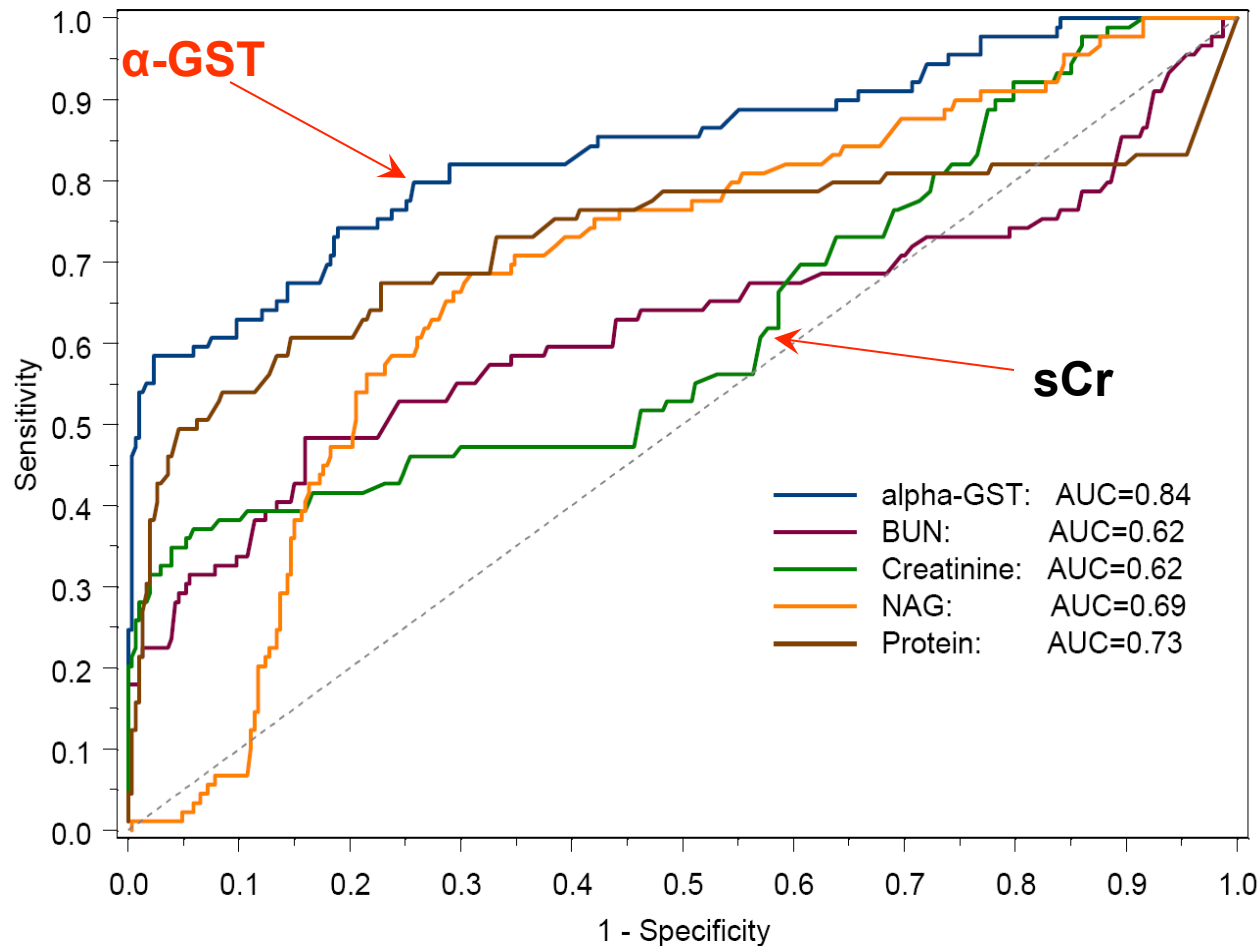
Numbers of rats

Controls
340
Received toxin
56

Courtesy of Pat Harlow, PhD, DCRP (information in ILSI-HESI publication: Harpur E, Ennulat D, Hoffman D, et al.; On behalf of the HESI Technical Committee on Biomarkers of Toxicity, Nephrotoxicity Working Group. Biological Qualification of Biomarkers of Chemical-induced Renal Toxicity in Two Strains of Male Rat. Toxicol Sci. 2011 May 18)



ROC analysis: PT degeneration or necrosis α -GST versus BUN, sCr, NAG, and protein

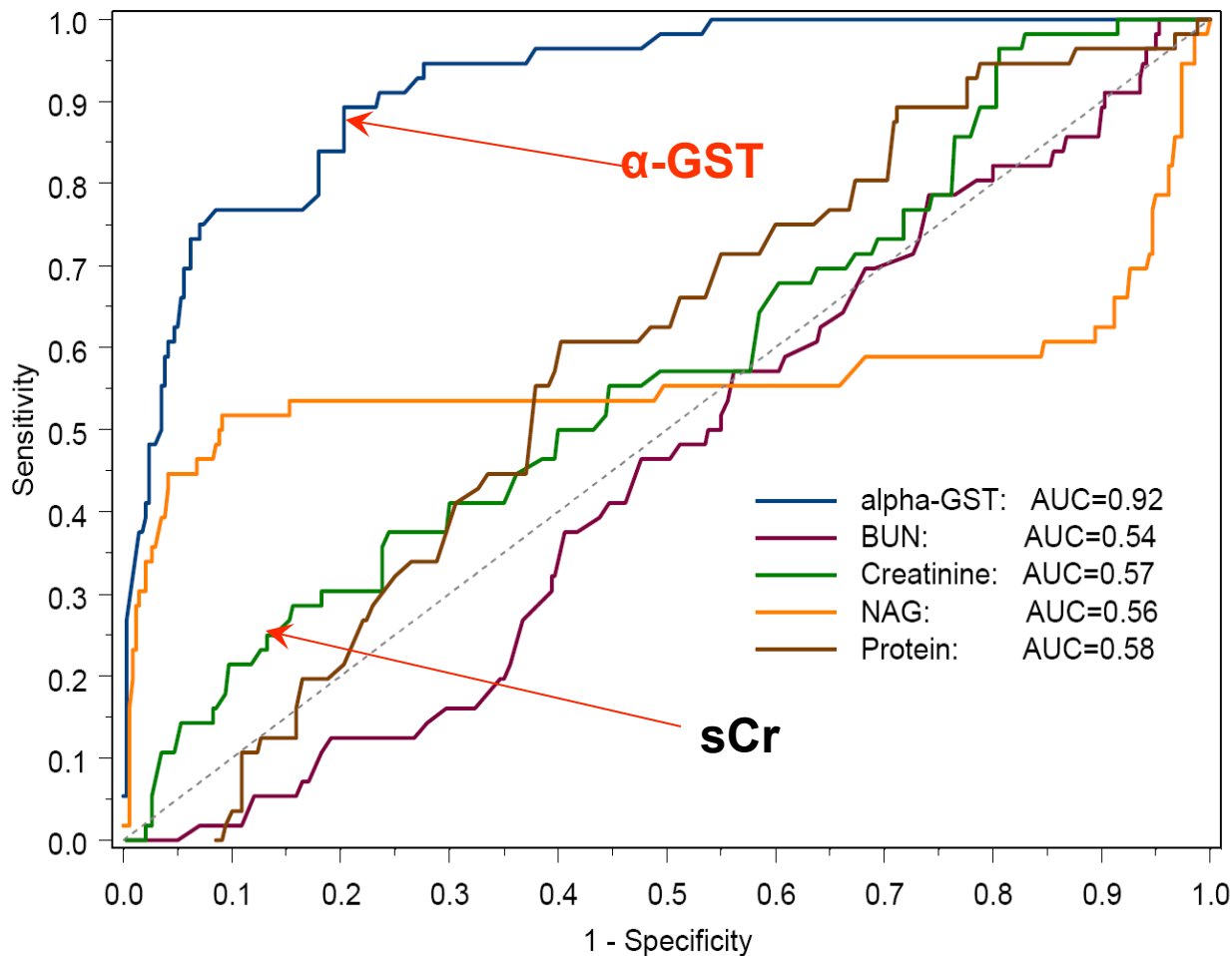


**α -GST increases
when there is
Proximal tubular
injury**

Courtesy of Pat Harlow, PhD, DCRP (adapted from ILSI-HESI publication: Harpur E, Ennulat D, Hoffman D, et al.; On behalf of the HESI Technical Committee on Biomarkers of Toxicity, Nephrotoxicity Working Group. Biological Qualification of Biomarkers of Chemical-induced Renal Toxicity in Two Strains of Male Rat. Toxicol Sci. 2011 May 18)

● ● ●

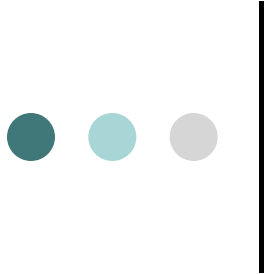
ROC analysis: CD degeneration or necrosis α -GST versus BUN, sCr, NAG, and protein



	Number of rats
Controls	340
Exposed to toxin	56

Paradoxically, α -GST decreases when there is Collecting Duct injury

Courtesy of Pat Harlow, PhD, DCRP (adapted from ILSI-HESI publication: Harpur E, Ennulat D, Hoffman D, et al.; On behalf of the HESI Technical Committee on Biomarkers of Toxicity, Nephrotoxicity Working Group. Biological Qualification of Biomarkers of Chemical-induced Renal Toxicity in Two Strains of Male Rat. Toxicol Sci. 2011 May 18



Excerpt from Dr. Woodcock's CDER
Qualification Letter for ILSI-HESI of Sept 22,
2010 (from ILSI-HESI website)

I. Qualification Decision and Context of Use

We have completed our review of this submission and conclude that:

- Urinary **Clusterin** and Renal Papillary Antigen (**RPA-1**) are **qualified biomarkers** for the context of use described below.
- **Alpha-glutathione S-transferase (α -GST)** is not qualified at this time.

Urinary Clusterin

Urinary Clusterin was previously qualified by FDA April 14, 2008. The data from this submission support the prior conclusions and clarify the context of use¹ as follows:

Urinary Clusterin is a qualified biomarker for voluntary use in the detection of acute drug-induced renal tubule alterations, particularly when regeneration is present, in male rats when used in conjunction with traditional clinical chemistry markers and histopathology in GLP toxicology studies for drugs for which there is previous preclinical evidence of drug induced nephrotoxicity or where it is likely given the experience with other members of the pharmacologic class.



Excerpt from Dr. Woodcock's CDER
Qualification Letter for ILSI-HESI (from
ILSI-HESI website)

Renal Papillary Antigen-1 (RPA-1)

Urinary RPA-1 is a novel biomarker not previously qualified. The data from this submission support the context of use as follows:

Urinary RPA-1 is a qualified biomarker for voluntary use in detecting acute drug-induced renal tubule alterations, particularly in the collecting duct, in male rats when used in conjunction with traditional clinical chemistry markers and histopathology in GLP toxicology studies for drugs for which there is previous preclinical evidence of drug induced nephrotoxicity or where it is likely given the experience with other members of the pharmacologic class.



Excerpt from Dr. Woodcock's CDER Qualification Letter for ILSI-HESI (from ILSI-HESI website

8. With respect to the **clinical use**, urinary clusterin and RPA-1 can be explored when and if sufficiently validated assays become available. At present, **urinary clusterin and RPA-1 are not currently qualified as primary renal injury monitoring tests or to define dose-stopping criteria in clinical drug development studies. For the time being, sponsors and regulatory divisions should decide on a case-by-case basis how best to explore and/or make use of these biomarkers in a clinical development program.**



Evolution of Qualification

- Requiring: A more specific context of use for the biomarkers including a proposed decision tree
- Requesting without requirements
 - Evaluation of temporal correlation between biomarker levels and the emergence of the histopathologic alterations.
 - Evaluation of biomarker performance during the recovery phase
 - Evaluations of renal biomarker performance in the setting of extrarenal organ injury
 - More thorough analyses of biomarker performance with toxins that cause different site-specific injury



Future Directions

- Clinical and more preclinical submissions:
 - AKI and chronic renal disease submissions
 - Hurdles
 - Financing
 - Biomarker Banks
 - Sharing information
 - Shared/ Not shared interactive databases



Biomarker Proposal for Clinical Trials

- Challenges stem mostly from the lack of a histopathology to use as a truth standard
- Nevertheless, trials are proceeding using creative methods
- Context of use has been proposed

Decision Tree for Clinical Use of Qualified Renal Biomarker(s)



Preclinical histopathology finding of renal tubular damage

Translational safety BMs

Preclinical BM pattern renal tubular injury

Renal tubular BM in SAD
First in Human Study

Renal injury pattern?

Yes

Consider discontinuation or restricted development

No

Renal tubular BM in MAD
Healthy Volunteer Study

Renal injury pattern?

Yes

Consider discontinuation or restricted development

No

Small controlled patient study

Renal injury pattern? sCR/BUN +/- BM

Yes

Consider discontinuation or restricted development

No

Large outpatient studies in broad patient population(s)

Courtesy of PSTC Nephrology Working Group and FNIH Biomarker Consortium



Contact Information

- Melanie Blank, MD:
melanie.blank@fda.hhs.gov
- For questions regarding submission of a Qualification Package: Marianne Noone: marianne.noone@fda.hhs.gov



Summary Slide

- Discussed:
 - Many potential contexts in which novel renal biomarkers may prove to be useful in preclinical and clinical trials
 - 2 successful examples of collaborations between consortia, FDA and EMA
 - An example of the importance of testing novel biomarkers with drugs that cause different site-specific renal injury
 - How moving ahead we are requiring details on the proposed context of use including decision trees for qualification submissions