FR-PO724

Development of a Treatment Response Prediction Strategy for Sparsentan in Glomerular Disease

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DISCLOSURES

- **MK, FE, LM, SE:** Grant, Travere Therapeutics.
- **MK, SE:** Other grants administered through the University of Michigan from Astra Zeneca, Novo Nordisk, Janssen Pharmaceuticals, Gilead Sciences, Inc., Eli Lilly and Company, Angion Biomedica, Ionis Pharmaceuticals, Inc., Moderna Therapeutics, Certa Therapeutics, Boehringer Ingelheim, Chinook Therapetuics, Regeneron Pharmaceuticals, American Foundation for AIDS Research.
- **LM:** Consultancy, Travere Therapeutics, Reata Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics.
- **BG, VN, WJ:** Nothing to disclose.
- **CJ, PB, RK:** Employees, Travere Therapeutics, Inc.

- Sparsentan is a first in-class, novel, dual endothelin angiotensin receptor antagonist (DEARA) being developed for the treatment of FSGS and IgA nephropathy
- The ADR-induced nephropathy rat model is characterized by rapid podocyte injury, proteinuria, glomerulosclerosis, tubulo-interstitial fibrosis, and lesions reflective of human FSGS

Aim

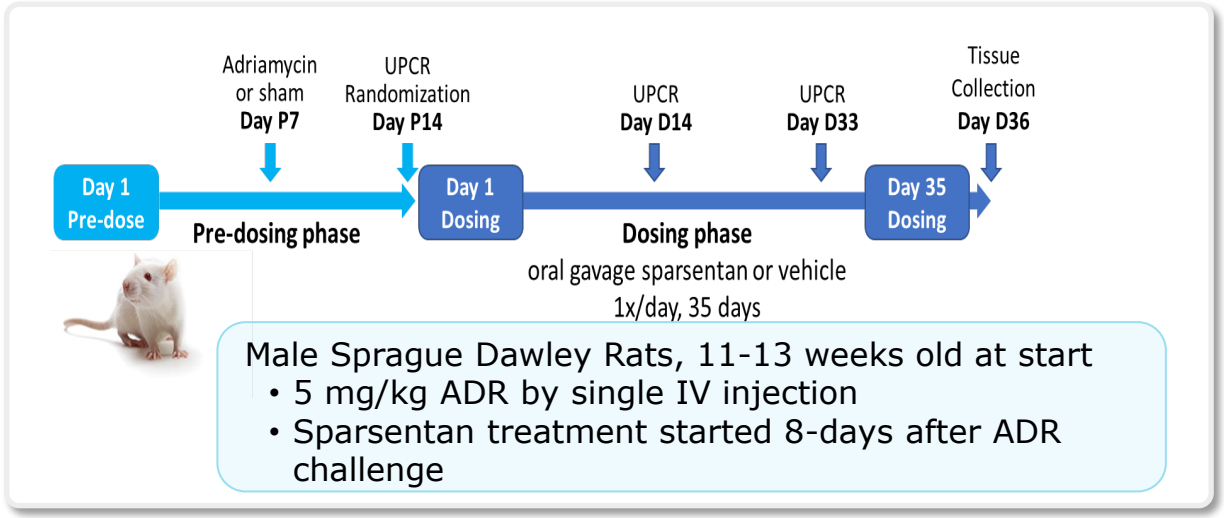
- To identify a transcriptional response profile to sparsentan in the ADR rat model that is translatable to human glomerular disease and that allows interrogation of non-invasive surrogate biomarkers

ADR, adriamycin; FSGS, focal segmental glomerulosclerosis.

METHODS

ADR Rat Model of FSGS

- RNA extracted from FFPE kidney tissue, sequenced and aligned to Rnor genome assembly version 6.0.88
- DEGs calculated with DESeq2 across comparisons between Sham (healthy), ADR (disease model) and ADR with sparsentan (treatment model)
- DEGs induced in the ADR model and suppressed by sparsentan were carried forward for human ortholog mapping (Ensembl build 104)



Clinical Data in Patients With FSGS (NEPTUNE Cohort)

- Human transcriptional profiles were generated from microdissected glomerular and tubulointerstitial profiles from the NEPTUNE cohort
- Sparsental response scores were calculated using the average profile of the aforementioned genes

ADR, adriamycin; DEGs, differentially expressed genes; FFPE, formalin fixed paraffin embedded.

RESULTS

Sparsentan Attenuated Measures of Disease Severity in the Rat ADR Model of FSGS

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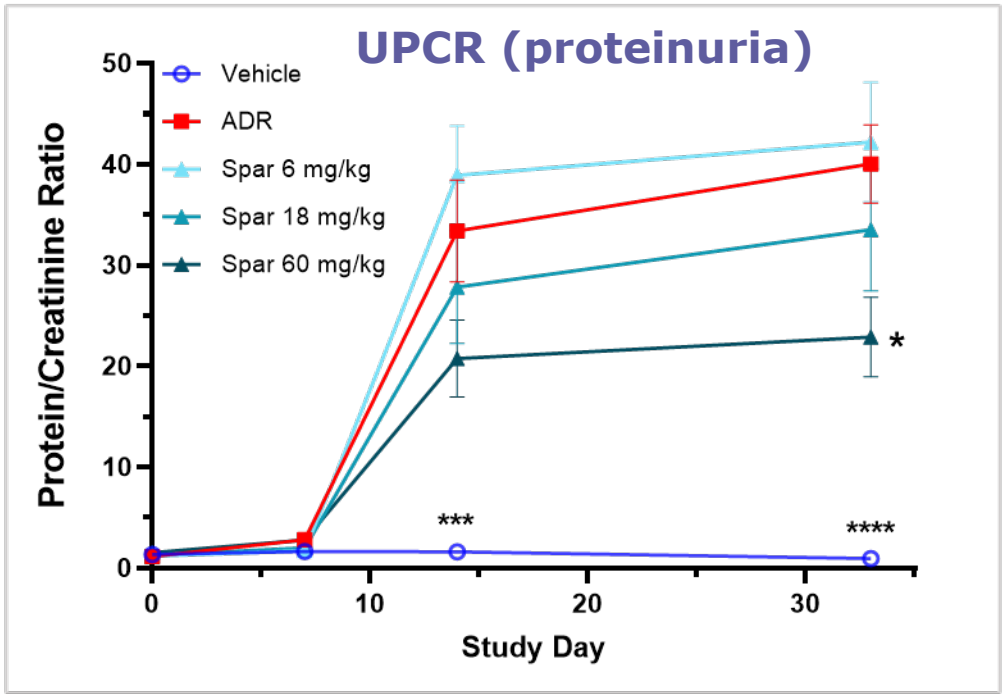

Two-Way ANOVA mixed Model ****p<0.0001; ***p=0.0005; *p=0.0215 vs. ADR.

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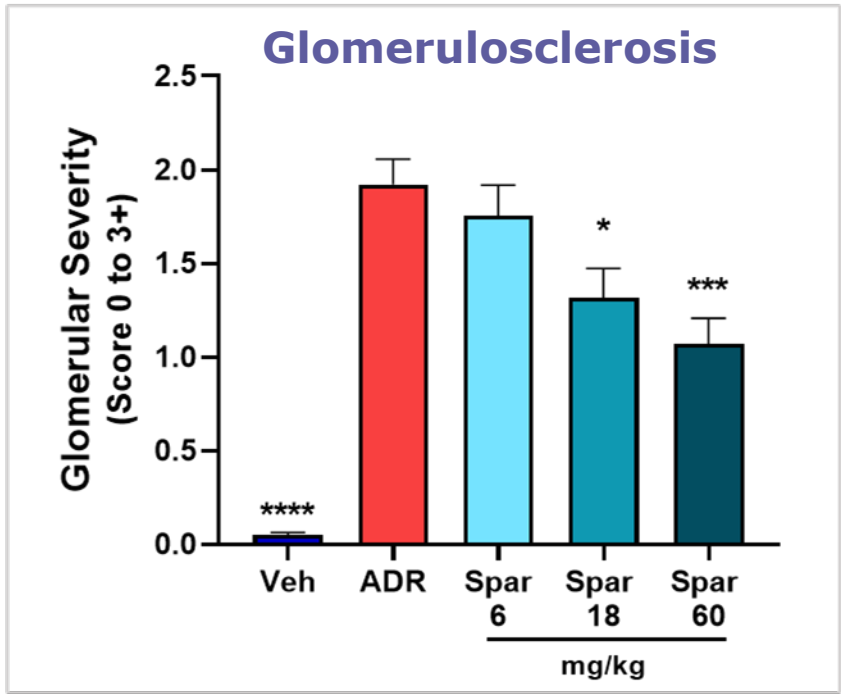

One-Way ANOVA ****p<0.0001; ***p=0.0005; *p=0.0155 vs. ADR.

- UPCR and glomerulosclerosis were dose-dependently reduced, with significant attenuation at the high dose of 60 mg/kg.

ADR, adriamycin; FSGS, focal segmental glomerularsclerosis; UPCR, urine protein-creatinine ratio.

RESULTS

High Dose Sparsentan Treatment Reversed Directionality of Many Genes Induced in the Model, Disease-Associated Network Activities, and was Consistent with Angiotensin Blockage

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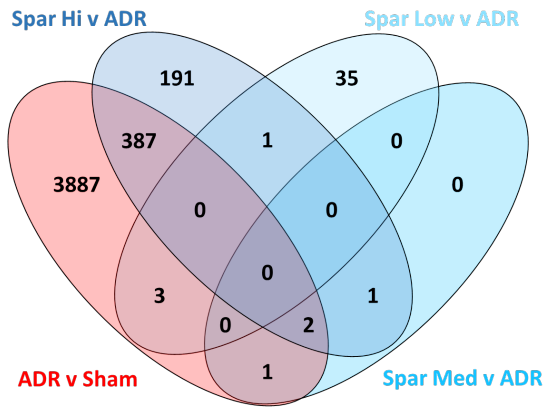

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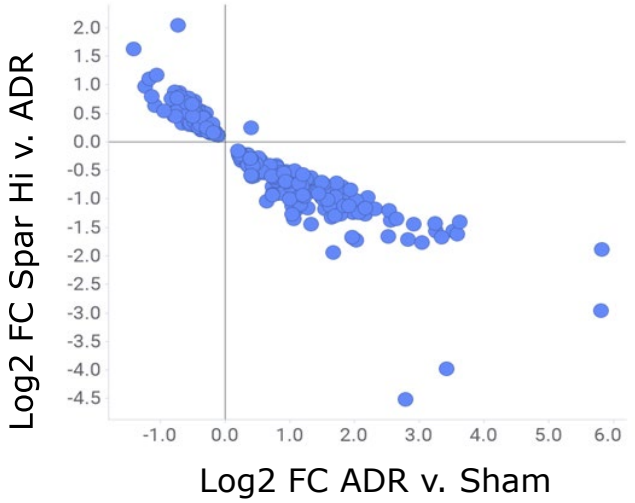


C

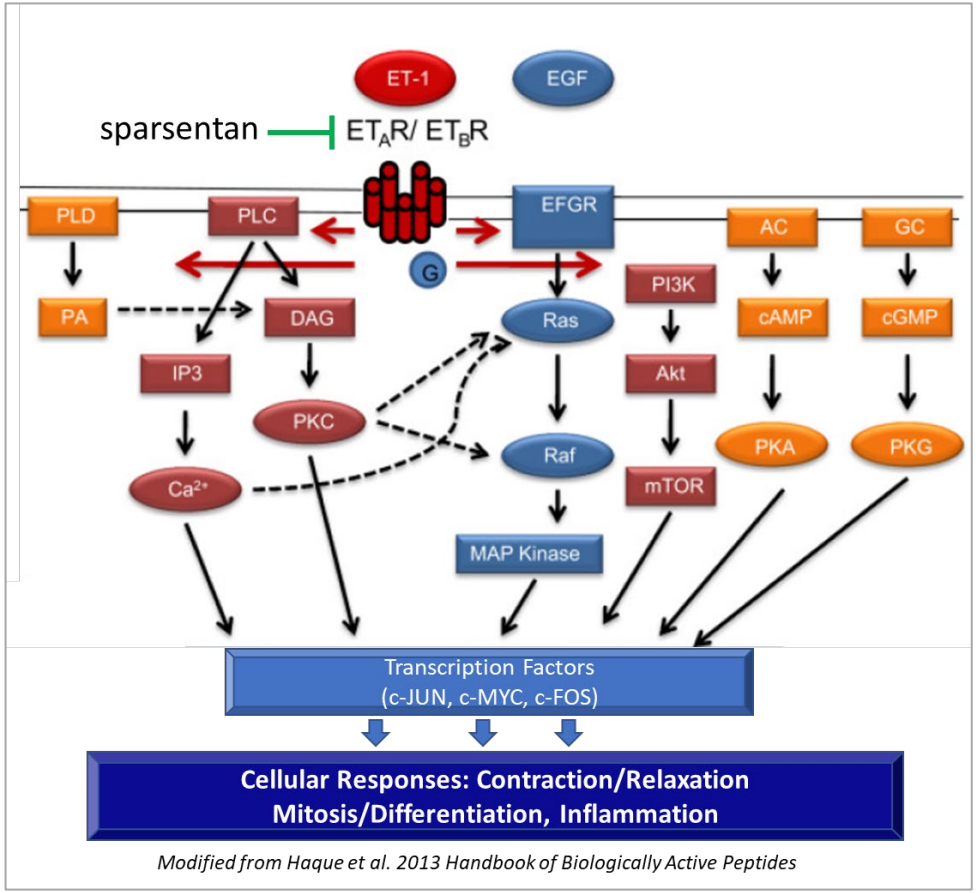
	Predicted Activity	
Upstream regulator	ADR v. Sham	Spar Hi v. ADR
TNF	11.2	-5.7
IL1B	8.2*	-4.6*
AGT	9.9	-4.5
IFNG	10.0	-3.5
JAK1	4.5*	-2.4*

*Gene was differentially regulated in the comparison consistent with predicted activity.
DEG profiles (p-adj<0.05) were consistent with measures of disease progression in rats; networks identified from DEG profiles were consistent with pathways activated and implicated in human FSGS. Sparsentan attenuated predicted increases in network activities of AGT (angiotensinogen) consistent with mechanism of action.

RESULTS

A subset of Genes Reversed by Sparsentan in the ADR Model were Enriched in the Endothelin Pathway

Symbol	Entrez Gene Name	ADR v. Sham log2 FC	Spar Hi v. ADR log2 FC
ADCY5	adenylate cyclase 5	-0.5	0.4
ADCY7	adenylate cyclase 7	1.1	-0.7
HMOX1	heme oxygenase 1	1.7	-1.9
JUN	Jun proto-oncogene, AP-1 transcription factor subunit	0.7	-0.4
MYC	MYC proto-oncogene, bHLH transcription factor	1.6	-1.1
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	-0.2	0.2
PIK3CD	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta	0.9	-0.6
PIK3R5	phosphoinositide-3-kinase regulatory subunit 5	1.2	-0.7
PRKCZ	protein kinase C zeta	-0.4	0.3
PTGS2	prostaglandin-endoperoxide synthase 2	-0.7	2.1
RASD1	ras related dexamethasone induced 1	1.2	-1.1



The 388 gene intersect between SparHi v. ADR and ADR v. Sham was enriched for endothelin pathway genes ($p<0.001$, Fisher's exact test). Pathway genes in both analyses that were significantly after multiple hypothesis correction are shown in the table.

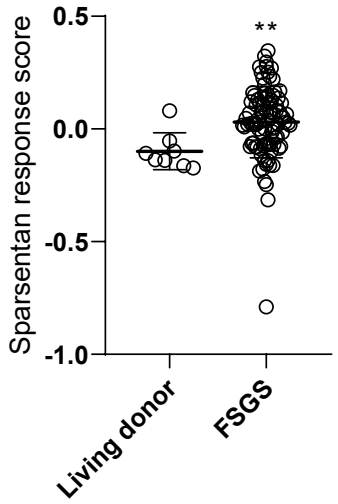
RESULTS

Sparsentan Responsive Genes were Associated with Human FSGS and Clinical Measures of Disease

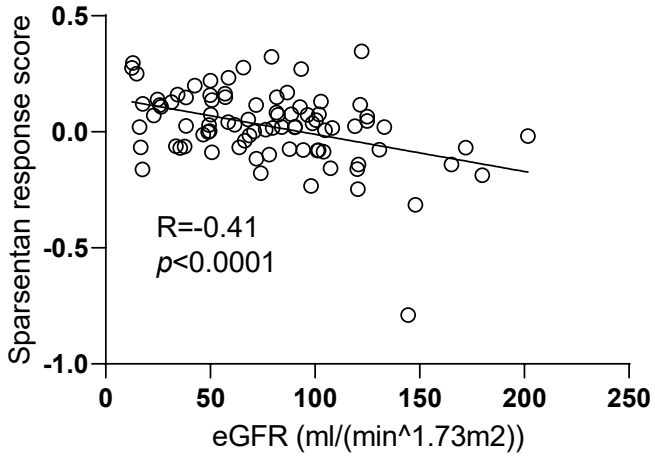
A **Clinical Information**

NEPTUNE cohort	FSGS
Samples with glom RNA-seq	93
Sex	59M/34F
Age (mean ± SD)	30 ± 22
eGFR at Bx (mean ± SD)	75 ± 38
UPCR (median, IQR)	2.7, 5.4

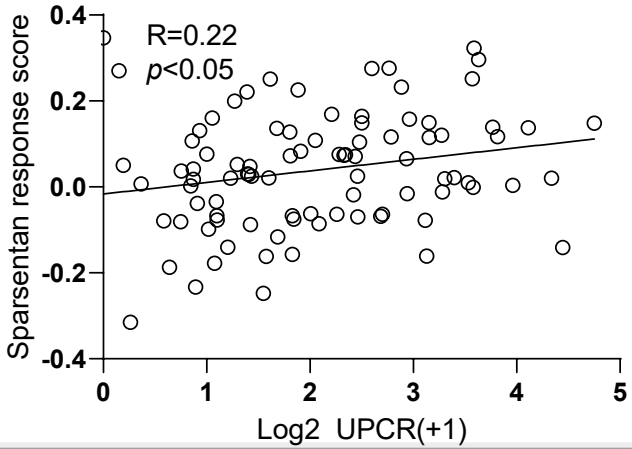
B **Sparsental Response Score Elevated in Patients with FSGS Compared with Healthy Living Transplant Donors**



C **Sparsental Response Score Negatively Correlated with eGFR at Time of Biopsy**



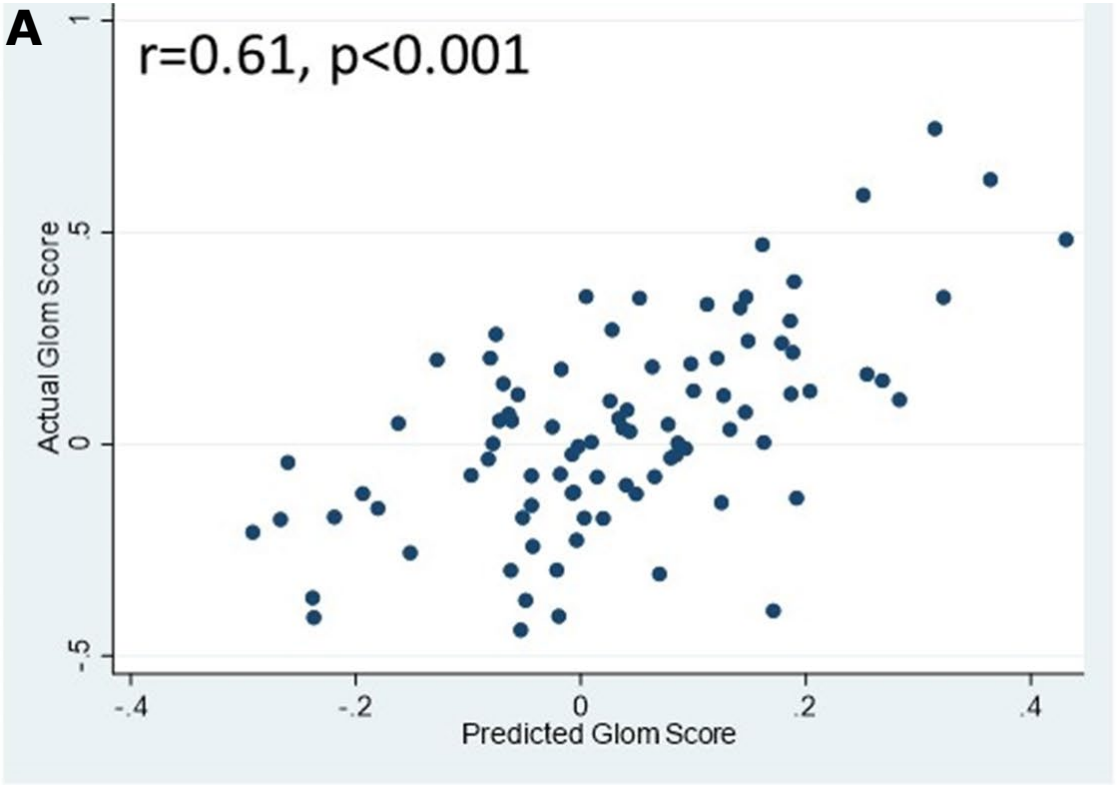
D **Sparsental Response Score Positively Correlated with UPCR at Time of Biopsy**



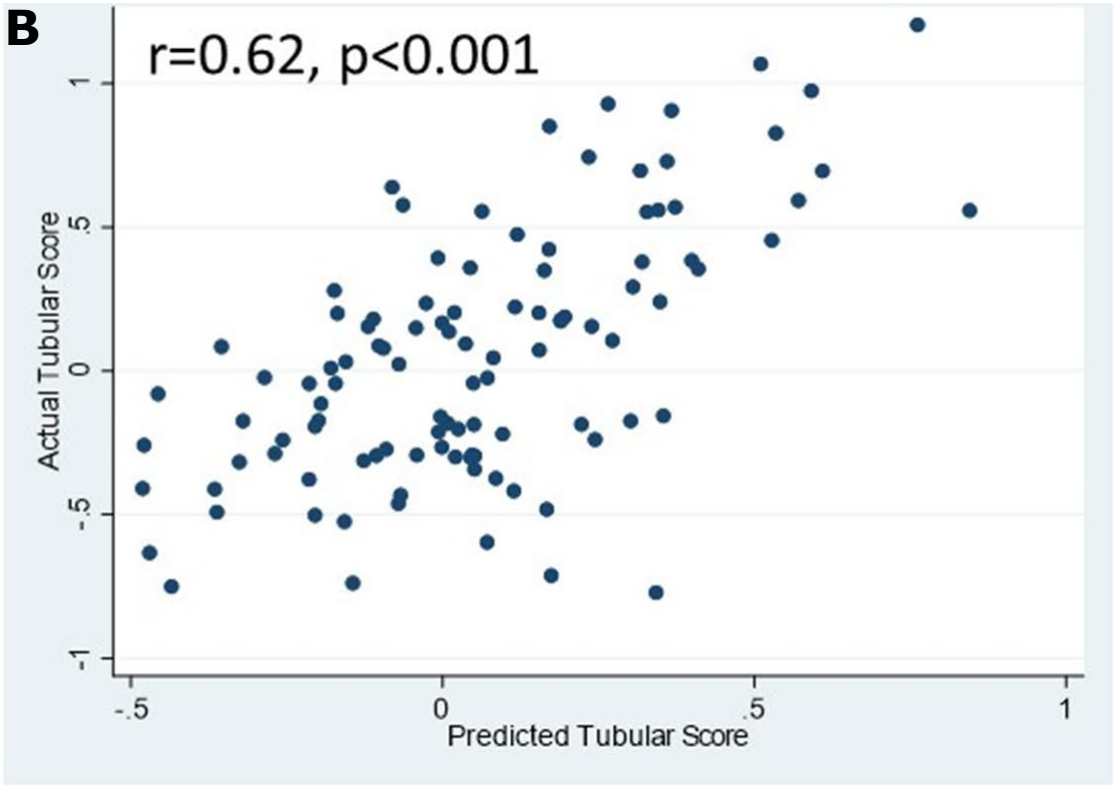
Human orthologs of genes suppressed by sparesentan in the Spar Hi vs ADR comparison were Z-transformed and the average of all genes was used to compute an intrarenal sparsentan response score from glomerular transcriptomes.

Biomarkers Identified from Urine (uA2M/Cr) and Plasma (PDGFB), Along with eGFR and UPCR, Predicted Sparsentan Response Scores

Correlation between predicted and calculated sparsentan scores in glomeruli (uA2M/Cr, PDGFB, eGFR in the predicted model)



Correlation between predicted and calculated sparsentan scores in tubulointerstitium (uA2M/Cr, PDGFB, eGFR, UPCR in the predicted model)



Cr, creatinine; eGFR, estimated glomerular filtration rate; PDGFB, plasma derived growth factor-beta; UPCR, urine protein-creatinine ratio.

CONCLUSIONS

- Sparsentan treatment of an ADR rat model impacted expected target pathways (angiotensin and endothelin)
- Sparsentan treatment also impacted pathways implicated in FSGS (e.g., TNF, JAK-STAT)
- A response score was elevated in patients with FSGS from the NEPTUNE cohort and associated with routine clinical measures
- Biomarkers and clinical measures (eGFR and UPCR) were able to predict intrarenal transcriptional profiles of genes responsive to sparsentan from animal models and are being further evaluated

ADR, adriamycin; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; TNF, tumor necrosis factor; UPCR, urine protein-creatinine ratio.

ACKNOWLEDGMENTS

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NIH National Institute of Diabetes and Digestive and Kidney Diseases

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