Histologic and Molecular Correlates in Patients with AL Amyloidosis in Remission But With Persistent Renal Disease

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International Kidney and Monoclonal Gammopathy

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AL Amyloidosis

- Complete hematologic responses can suppress LC production but organ responses are **heterogeneous**

- There is a lack of insight on the mechanisms by which amyloid deposits drive alterations in the kidney **anatomically and functionally**

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RAIN: Renal AL-amyloidosis Involvement and NEOD001

- Phase 2B multicenter trial that was to enroll 100 patients with:
  - Persistent proteinuria (>500mg per day)
  - Previously attained a stable hematologic response to prior anti-plasma cell therapy
- All participants were to undergo a **kidney biopsy** prior to randomization to receive placebo or NEOD001*

* **M**onoclonal antibody that targets amyloid fibrils deposited within organs

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Ancillary Studies

1) **Transcriptional Profiling**

2) **Histologic Scoring**

   – ***Injury score***

   – ***Amyloid score***

Hypothesis:

Specific signatures of gene expression can be mapped back to certain histologic features

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Objective

To ***identify genes*** that regulate the **molecular pathways** that make regeneration of renal tissue less or more likely

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Apr 23, 2018

Prothena Discontinues Development Of NEOD001 For AL Amyloidosis

- **Phase 2b PRONTO study did not meet its primary or secondary endpoints**
- **Phase 3 VITAL Amyloidosis Study being discontinued based on futility analysis**
- **Investor conference call and webcast today at 8:30 AM ET**

Baseline Characteristics

Patient ID	Heme status	Creatinine	eGFR	24h urinary protein (mg)	Renal stage (1-3)
1	VGPR	0.90	101	3645	1
2	VGPR	1.90	42	3249	2
3	CR	1.80	43	6121	3
4	VGPR	1.12	76	17032	2
5	VGPR	1.28	68	5810	2
6	VGPR	0.88	71	1610	1
7	VGPR	0.80	82	4023	1
8	PR	1.14	62	3367	1
9	VGPR	1.23	64	9339	2
10	VGPR	1.00	72	6338	2

Histologic Scoring

- 2 ***expert*** renal pathologists blinded to baseline characteristics

Amyloid Score (AS)

Composite Scarring Injury Score (CSIS)

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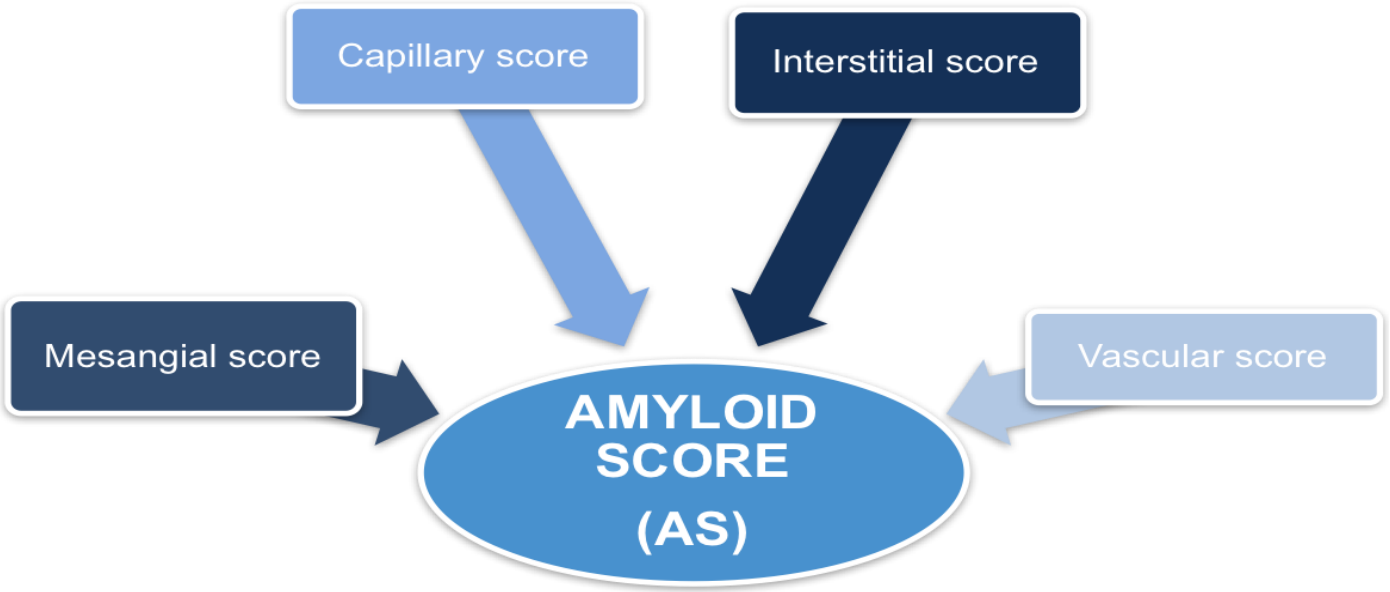
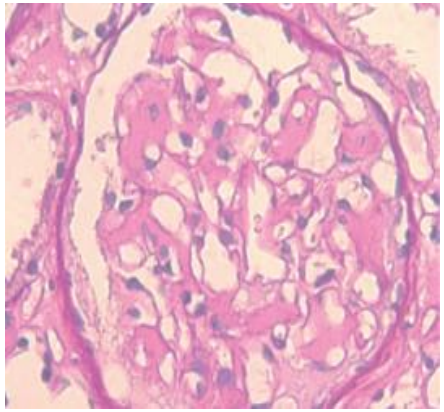
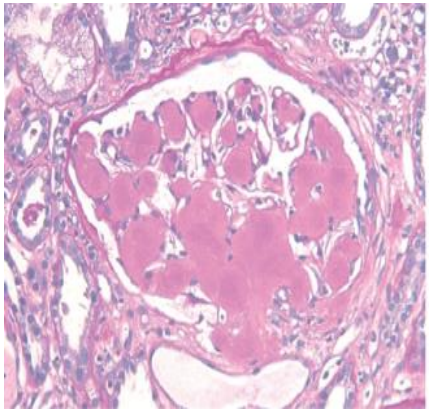
Amyloid Score







- 0 = absent
- 1+ = minimal; < 25%
- 2+ = moderate; 25-50%
- 3+ = severe; >50%

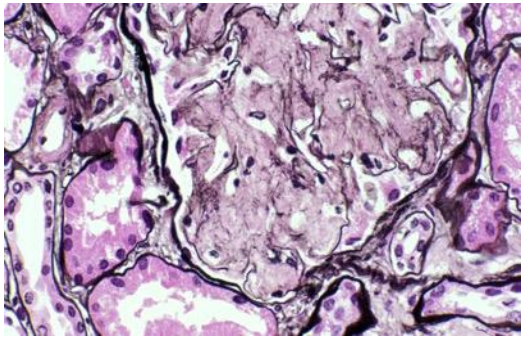
** The sum of scores generates the **Amyloid Score** (**max score of 12**)

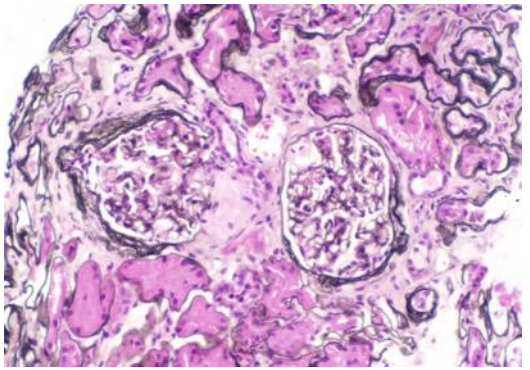
Composite Scarring Injury Score

Average tubulointerstitial fibrosis %

% global and segmental sclerosis

COMPOSITE SCARRING INJURY SCORE (CSIS)

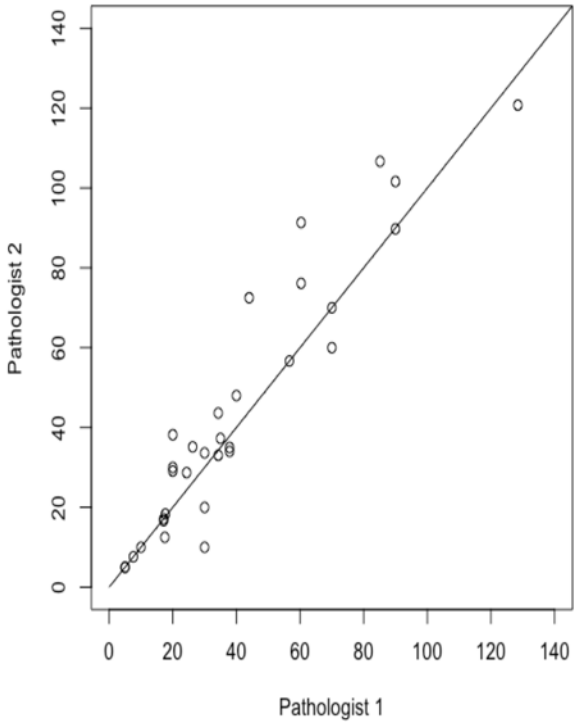




** The sum of scores generates the **CSIS** (**max score of 200**)

Interobserver Agreement Score

CSIS



Pearson's correlation = 0.94

AS

Cross Tabulations

	3	4	5	6	7	8	9	10	11	12
3	2	3	0	0	0	0	0	0	0	0
4	1	0	2	0	0	0	0	0	0	0
5	0	0	0	1	0	0	0	0	0	0
6	0	0	0	1	2	0	1	0	0	0
7	0	1	0	1	1	2	0	2	0	0
8	0	0	0	0	1	3	0	1	1	0
9	0	0	0	0	0	0	0	1	1	1
10	0	0	0	0	0	0	0	0	1	1

Spearman's correlation = 0.86

Transcriptional Profiling

- 10 kidney biopsy cores were received at Michigan Kidney Translational Medicine Core lab
  - Dissected into glomerular and tubular compartments
  - Total RNA was extracted and sequenced to generate gene expression profiles

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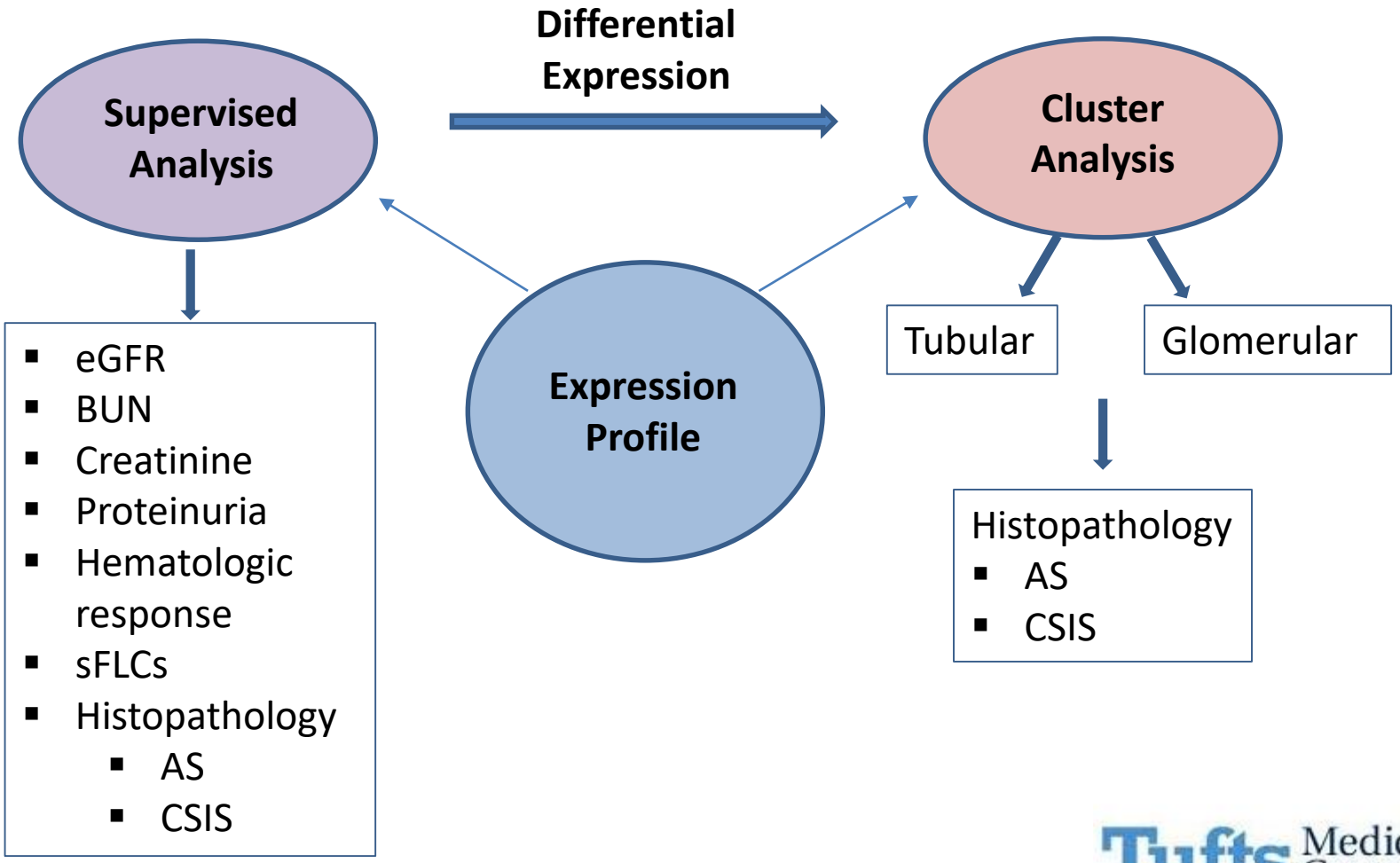
Methods



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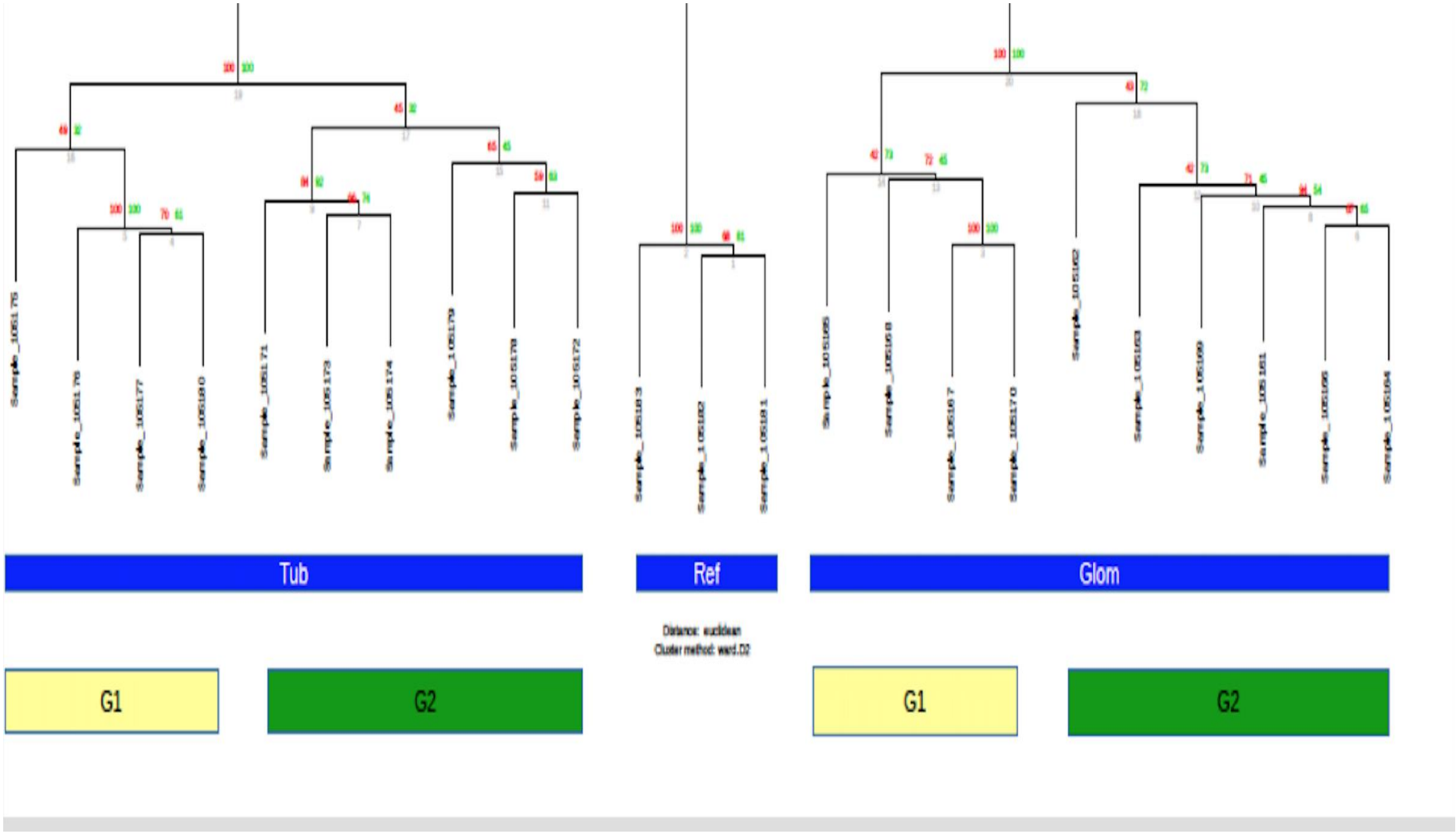
Tub
Ref
Glom
Distance: euclidean
Cluster method: ward.D2
G1
G2
G1
G2

G1 vs. G2

- Tubular
  - **AS (4.25 vs. 7.00) p = 0.03**
    - Interstitium (0.125 vs 0.83) p = 0.04
  - CSIS (16.75 vs. 32.8) p = 0.16
- Glomerular
  - **AS (4.38 vs. 6.92) p = 0.04**
    - Mesangium (1.50 vs. 2.75) p = 0.03
  - CSIS (17.65 vs. 32.2) p = 0.21

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Genes of Interest

Genes	G1	G2	Function
Tubular			
IQCD	+	-	Unknown
SF3A2	+	-	Splicing factor
ASPHD1	+	-	Peptidyl-amino acid modification
NSFLC1	-	+	Establishment of mitotic spindles, regrowth of Golgi, transport vesicle
ZSCAN30	-	+	DNA-binding transcription
VSIG8	-	+	RNA binding
JRK	-	+	DNA binding, mRNA binding
Glomerular			
PODXL	+	-	Cell adhesion, regulation of microvillus assembly

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All associations significant at q value <= 0.1

Future Investigations

- Validate expression patterns by IHC staining
  - RAIN biopsies
  - Repository AL biopsies
- Compare expression data to controls and other nephropathies in NEPTUNE data set
- Multicenter trial – prospective

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