Novel Biomarkers of Cisplatin-induced Kidney Damage

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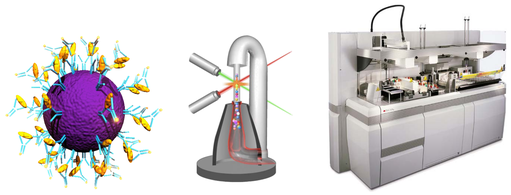


Introduction

In 2008, the FDA and EMEA issued a joint framework allowing for the biomarker qualification and regulatory endorsement of 7 new urinary biomarkers of drug-induced kidney injury in rats. We sought to screen for other novel biomarkers of drug induced kidney injury by utilizing the original Novartis study samples that were the source for the Predictive Safety Testing Consortium's (PSTC) submission to the FDA and EMEA.

Methods

Control and Cisplatin study samples with previously documented proximal tubular injury were utilized to investigate novel biomarker candidates. Urine was collected at termination days 3, 7, 14 and 21, plasma at days 1, 3, 7, 21. Histopathology was performed with a standardized hierarchical lexicon. A panel of 58 protein biomarkers comprising cytokines, inflammatory markers, growth factors, and tissue factors were quantified in urine and plasma samples with the RBM RodentMAP® v2.0 multiplex immunoassay service. Performance of biomarker candidates from the panel was assessed with a Receiver Operating Characteristic (ROC) analysis.

RodentMAP® v2.0 | Antigens

1. Apolipoprotein A1
2. C-Reactive Protein
3. CD40
4. CD40 Ligand
5. Endothelin-1
6. Eotaxin
7. Epidermal Growth Factor
8. Factor VII
9. Fibrinogen
10. FGF-basic
11. FGF-9
12. GCP-2
13. GM-CSF
14. GST-alpha
15. Haptoglobin
16. Immunoglobulin A
17. Inducible Protein-10
18. Interferon-gamma
19. Interleukin-1 alpha
20. Interleukin-1 beta
21. Interleukin-2
22. Interleukin-3
23. Interleukin-4
24. Interleukin-5
25. Interleukin-6
26. Interleukin-7
27. Interleukin-10
28. Interleukin-11
29. Interleukin-12p70
30. Interleukin-17
31. KC/GRO alpha
32. Leukemia Inhibitory Factor
33. Lymphotactin
34. M-CSF
35. MDC
36. MIP-1 alpha
37. MIP-1 beta
38. MIP-1 gamma
39. MIP-2
40. MIP-3 beta
41. MMP-9
42. MCP-1
43. MCP-3
44. MCP-5
45. Myeloperoxidase
46. Myoglobin
47. Oncostatin M
48. RANTES
49. Serum Amyloid P
50. SGOT
51. Stem Cell Factor
52. Thrombopoietin
53. TIMP 1
54. Tissue Factor
55. Tumor Necrosis Factor-alpha
56. VCAM-1
57. VEGF
58. von Willebrand Factor

Results

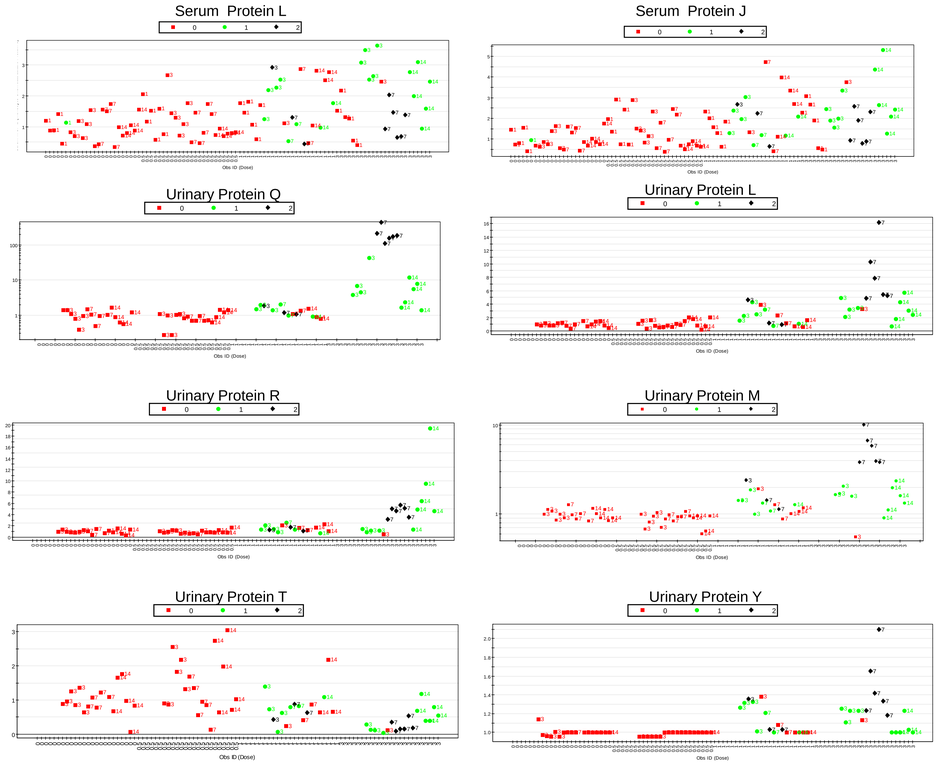
Several new biomarkers not linked to previously described kidney biomarkers were significantly increased in urine and plasma and correlated to histopathological kidney damage severity. In addition, ROC analysis indicated that several of the novel analytes are sensitive and specific markers of drug-induced kidney damage with a significantly higher AUC of ROC than BUN and serum Creatinine.

ROC Analyses

Biomarker (Blinded)	Medium	Norm	Analysis Type	AUC	AUC Stdev	Dir	Thrld	Spec	Sens	N Ctrls	N Injur
Serum Creatinine	Serum		Exclusion	0.527	0.082	1	1.075	1.000	0.286	23	28
			Inclusion	0.586	0.065	1	1.065	0.955	0.276	67	29
BUN	Serum		Exclusion	0.615	0.079	-1	0.850	0.957	0.357	23	28
			Inclusion	0.520	0.065	-1	0.751	0.955	0.103	67	29
Protein J	Serum		Exclusion	0.845	0.055	1	1.764	0.957	0.643	23	28
			Inclusion	0.683	0.062	1	3.364	0.955	0.103	67	29
Protein K	Serum		Exclusion	0.828	0.058	1	1.149	0.957	0.536	23	28
			Inclusion	0.712	0.061	1	1.276	0.955	0.310	67	29
Protein L	Serum		Exclusion	0.781	0.064	1	1.592	0.957	0.571	23	28
			Inclusion	0.695	0.061	1	2.773	0.955	0.207	67	29
Protein M	Serum		Exclusion	0.762	0.066	1	1.417	0.957	0.571	23	28
			Inclusion	0.689	0.062	1	2.088	0.955	0.207	67	29
Protein N	Serum		Exclusion	0.792	0.063	1	1.397	0.957	0.5	23	28
			Inclusion	0.682	0.062	1	2.096	0.955	0.207	67	29
Protein O	Urine		Exclusion	0.846	0.059	1	1.413	1.000	0.538	17	26
			Inclusion	0.827	0.055	1	1.413	0.951	0.538	41	26
Protein P	Urine	UCrea	Exclusion	0.826	0.062	1	2.229	1.000	0.385	17	26
			Inclusion	0.845	0.053	1	1.524	0.952	0.654	42	26
Protein Q	Urine	UCrea	Exclusion	0.910	0.046	1	1.846	1.000	0.680	16	25
			Inclusion	0.922	0.039	1	1.656	0.974	0.720	39	25
Protein L	Urine	UCrea	Exclusion	0.889	0.050	1	1.574	1.000	0.808	17	26
			Inclusion	0.861	0.050	1	2.417	0.952	0.654	42	26
Protein M	Urine	UCrea	Exclusion	0.871	0.054	1	1.470	1.000	0.769	17	26
			Inclusion	0.845	0.053	1	2.281	0.952	0.538	42	26
Protein R	Urine	UCrea	Exclusion	0.844	0.059	1	1.755	1.000	0.538	17	26
			Inclusion	0.831	0.055	1	2.117	0.952	0.500	42	26
Protein S	Urine	UCrea	Exclusion	0.837	0.060	1	1.930	1.000	0.500	17	26
			Inclusion	0.855	0.051	1	1.738	0.952	0.577	42	26
Protein T	Urine	UCrea	Exclusion	0.819	0.064	-1	0.040	1.000	0.038	17	26
			Inclusion	0.796	0.059	-1	0.138	0.952	0.192	42	26
Protein U	Urine	UCrea	Exclusion	0.894	0.049	1	1.567	1.000	0.538	17	26
			Inclusion	0.877	0.048	1	1.588	0.952	0.500	42	26
Protein V	Urine		Exclusion	0.833	0.061	-1	0.144	1.000	0.154	17	26
			Inclusion	0.715	0.066	-1	0.286	0.952	0.154	42	26
Protein W	Urine		Exclusion	0.934	0.038	1	1.280	1.000	0.808	17	26
			Inclusion	0.934	0.036	1	1.280	0.952	0.808	42	26
Protein X	Urine		Exclusion	0.846	0.059	1	1.356	1.000	0.462	17	26
			Inclusion	0.810	0.057	1	1.423	0.951	0.346	41	26
Protein Y	Urine		Exclusion	0.887	0.050	1	1.183	1.000	0.577	17	26
			Inclusion	0.870	0.049	1	1.144	0.952	0.577	42	26

Plots

The plots show the biomarker levels for all samples investigated. All values are represented as fold-changes. The animals are ordered by dose-group (with increasing doses) and within each dose-group by termination time point (with increasing time). The symbols and the colors represent the histopathology readout for proximal tubular damage for the corresponding animal (red = no histopathology finding observed, green = grade 1, black = grade 2 on a 5 grade scale). The data point labels represent the termination time point and the x-axis labels represent the dose level



Conclusions

The newly identified biomarkers have potential to complement the already known and partially qualified biomarkers for drug induced kidney injury in particular for monitoring inflammatory processes, whereas the 7 endorsed biomarkers are mechanistically linked to functional changes, cell injury and regeneration processes.