Pre-clinical Evaluation of Biomarkers for the Early Detection of Nephrotoxicity Following Alpha-particle Radioligand Therapy

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Supplemental Table 1. Scoring Criteria for Kidney Histological Changes

Tubular Injury Scoring		Glomerular Changes	
0	Absent	0	Absent
1	Mild (1-10%)	1	1-10%
2	Moderate (11-25%)	2	11-20%
3	Severe (26-50%)	3	21-30%
4	Very Severe > 50%	4	31% and greater

Tubulointerstitial Inflammation		Interstitial Fibrosis	
0	Absent	0	Absent
1	Mild (1-10%)	1	Mild (1-10%)
2	Moderate (11-25%)	2	Moderate (11-25%)
3	Severe (26-50%)	3	Severe (26-50%)
4	Very Severe > 50%	4	Very Severe > 50%

Supplemental Table 2. Ex vivo [^{203}Pb]Pb-MC1L biodistribution results for male CD-1 Elite mice (Units of percent injected dose per gram, corrected for [^{203}Pb] radioactive decay).

[^{203}Pb]Pb-MC1L Percent injected dose per gram (%ID/g)					
Tissue	**0.5 h**	**1.5 h**	**3.0 h**	**24 h**	**Avg. Organ Mass (g)**
Blood	1.37	0.06	0.01	0.02	3.000*
Heart	0.68	0.03	0.03	0.06	0.132
Lungs	2.15	0.19	0.12	0.08	0.173
Liver	0.64	0.40	0.49	0.32	1.409
Pancreas	0.50	0.04	0.13	0.57	0.023
Spleen	0.63	0.22	0.19	0.21	0.101
Stomach	0.86	0.08	0.11	0.06	0.423
Kidneys	8.30	4.88	4.51	1.99	0.467
Adrenals	1.31	0.34	0.27	0.42	0.011
Small Intestines	0.64	0.06	0.07	0.03	1.334
Large Intestine	0.86	0.06	0.10	0.06	1.379
Testes	0.41	0.07	0.03	0.05	0.183
Muscle	0.34	0.18	0.06	0.06	11.250**
Skin	1.12	0.22	0.12	0.13	5.625***
Bone	0.46	0.11	0.09	0.14	0.069
Brain	0.04	0.01	0.02	0.02	0.369
Eyes	0.40	0.08	0.23	0.12	0.032

* Assuming 8% of total body mass is blood.
** Assuming 30% of total body mass is muscle.
*** Assuming 15% of total body mass is skin.

Supplemental Table 3. Percent administered activity ([^{212}Pb]Pb-MC1L) per organ as a function of time, calculated from [^{203}Pb]Pb-MC1L ex vivo biodistribution data.

[^{212}Pb]Pb-MC1L percent administered activity per (%AA/organ)				
Tissue	**0.5 h**	**1.5 h**	**3.0 h**	**24 h**
Blood	3.978	0.163	0.025	0.013
Heart	0.086	0.004	0.003	0.002
Lungs	0.359	0.030	0.017	0.003
Liver	0.867	0.511	0.568	0.094
Pancreas	0.011	0.001	0.003	0.003
Spleen	0.061	0.020	0.016	0.004
Stomach	0.350	0.031	0.038	0.005
Kidneys	3.750	2.066	1.731	0.195
Adrenals	0.014	0.003	0.002	0.001
Small Intestines	0.830	0.073	0.077	0.008
Large Intestine	1.147	0.075	0.113	0.017
Testes	0.073	0.012	0.005	0.002
Muscle	3.659	1.836	0.555	0.141
Skin	6.098	1.122	0.555	0.153
Bone	0.031	0.007	0.005	0.002
Brain	0.016	0.003	0.006	0.002
Eyes	0.013	0.002	0.006	0.001

Supplemental Table 4. Bi-exponential fit parameters, and time-integrated activity coefficients for the two integration methods. τ1: Time-integrated activity coefficient calculated from the bi-exponential fit. τ2: time integrated activity coefficient calculated from trapezoidal integration assuming constant activity from 0 to 0.5 h, and physical decay beyond the terminal timepoint.

Fit coefficients:	A_1	λ_1	A_2	λ_2	τ_1	τ_2	τ_{avg}
Blood	21.164	3.356	0.026	0.029	0.0720	0.0478	0.0599
Heart	0.789	4.508	0.003	0.019	0.0034	0.0017	0.0026
Lungs	1.890	3.441	0.022	0.082	0.0081	0.0066	0.0074
Liver	12.640	7.763	0.063	0.072	0.0250	0.1033	0.0642
Pancreas	*	*	*	*	*	0.0011	0.0011
Spleen	0.178	2.878	0.019	0.066	0.0036	0.0038	0.0037
Stomach	2.598	4.226	0.037	0.068	0.0115	0.0096	0.0106
Kidneys	8.897	3.553	2.364	0.104	0.2524	0.3084	0.2804
Adrenals	0.043	2.555	0.002	0.033	0.0008	0.0007	0.0008
Small Intestines	5.745	4.067	0.080	0.078	0.0245	0.0200	0.0222
Large Intestine	11.872	4.853	0.101	0.060	0.0412	0.0297	0.0354
Testes	0.212	2.281	0.005	0.041	0.0022	0.0019	0.0021
Muscle	7.112	1.191	0.511	0.051	0.1600	0.1585	0.1593
Skin	17.542	2.330	0.645	0.060	0.1829	0.1771	0.1800
Bone	0.099	2.709	0.006	0.043	0.0017	0.0015	0.0016
Brain	0.243	6.130	0.005	0.031	0.0019	0.0013	0.0016
Eyes	0.462	7.928	0.004	0.046	0.0015	0.0011	0.0013

*Regression not well defined for Pancreas due to increase in estimated tissue concentration after 1.5 hours.

Supplemental Table 5. Summary of mouse and human organ masses and organ [^{212}Pb]Pb-MC1L time-integrated activity coefficients.

Tissue	m_{mouse} (g)	τ_{mouse} (MBq*h/MBq)	m_{human} (g)	τ_{human} (MBq*h/MBq)
Blood	3.000	5.99E-02	6364	2.42E-01
Heart	0.132	2.55E-03	330	8.61E-03
Lungs	0.173	7.38E-03	1200	8.14E-02
Liver	1.409	6.42E-02	1800	1.01E-01
Pancreas	0.023	1.13E-03	140	3.46E-03
Spleen	0.101	3.67E-03	150	4.30E-03
Stomach	0.423	1.06E-02	250	8.56E-03
Kidneys	0.467	2.80E-01	310	3.22E-01
Adrenals	0.011	7.77E-04	14	8.00E-04
Small Intestines	1.334	2.22E-02	350	8.41E-03
Large Intestine	1.379	3.54E-02	225	8.54E-03
Testes	0.183	2.06E-03	35	4.51E-04
Muscle	11.250	1.59E-01	29200	4.24E-01
Skin	5.625	1.80E-01	3600	1.32E-01
Bone	0.069	1.58E-03	4400	8.61E-02
Brain	0.369	1.59E-03	1450	5.36E-03
Eyes	0.032	1.28E-03	15	6.86E-04

Supplemental Table 6. Murine absorbed dose estimates by tissue for [^{212}Pb]Pb-MC1L, generated using OLINDA 2.2.

	Dose per administered activity (mGy/MBq)			
Tissue	**Alpha**	**Beta**	**Gamma**	**Total**
Brain	2.05E+01	7.46E+00	4.14E-01	2.84E+01
Large Intestine	1.67E+02	2.14E+01	7.75E-01	1.89E+02
Small Intestine	1.26E+02	1.76E+01	1.40E+00	1.45E+02
Stomach	1.64E+02	1.94E+01	3.48E-01	1.84E+02
Heart	1.37E+02	2.03E+01	1.15E+00	1.59E+02
Kidneys	2.76E+03	2.34E+02	3.18E+00	2.99E+03
Liver	2.09E+02	2.87E+01	1.41E+00	2.39E+02
Lungs	1.99E+02	1.52E+01	5.18E-01	2.14E+02
Pancreas	2.16E+02	2.89E+02	9.81E+00	5.15E+02
Skeleton	1.29E+02	5.30E+01	6.23E+00	1.88E+02
Spleen	1.06E+02	2.10E+01	1.23E+00	1.29E+02
Testes	4.98E+01	9.81E+00	5.21E-01	6.01E+01
Thyroid	4.91E+01	5.68E+00	4.97E-01	5.53E+01
Total Body	4.91E+01	1.14E+01	4.87E-01	1.14E+02
Blood*	8.98E+01	-	-	8.98E+01
Adrenals*	3.13E+02	-	-	3.13E+02
Muscle*	6.37E+01	-	-	6.37E+01
Skin*	1.44E+02	-	-	1.44E+02
Eyes*	1.78E+02	-	-	1.78E+02

* Blood, adrenals, muscle, skin, and eyes are not implemented as source/target tissues in the OLINDA 2.2 murine models, and therefore dose to these tissues was calculated assuming local alpha particle energy deposition, with an average alpha energy of 7.8063 MeV per [^{212}Pb] decay. Beta and gamma self-dose contributions were not calculated for these tissues.

Supplemental Table 7. Estimated human dosimetry for [^{212}Pb]Pb-MC1L.

Tissue	Alpha (mGy/MBq)	Beta (mGy/MBq)	Gamma (mGy/MBq)	Total (mGy/MBq)
Adrenals	2.62E-01	4.54E-02	3.26E-02	3.40E-01
Brain	1.69E-02	1.89E-03	2.07E-03	2.09E-02
Esophagus	4.70E-02	5.32E-03	7.24E-03	5.96E-02
Eyes	2.10E-01	2.17E-02	3.37E-03	2.35E-01
Gallbladder	4.70E-02	6.04E-03	1.14E-02	6.44E-02
Left Colon	4.70E-02	1.52E-02	9.92E-03	7.21E-02
Small Intestine	4.70E-02	1.16E-02	7.98E-03	6.65E-02
Stomach	4.70E-02	1.44E-02	8.87E-03	7.03E-02
Right Colon	4.70E-02	1.52E-02	8.96E-03	7.11E-02
Rectum	4.70E-02	5.29E-03	5.60E-03	5.78E-02
Heart	1.20E-01	1.36E-02	7.77E-03	1.41E-01
Kidneys	**4.76E+00**	**5.17E-01**	**5.91E-02**	**5.34E+00**
Liver	2.58E-01	2.90E-02	1.37E-02	3.01E-01
Lungs	3.11E-01	3.33E-02	7.02E-03	3.51E-01
Pancreas	1.13E-01	1.23E-02	1.03E-02	1.36E-01
Prostate	4.70E-02	5.29E-03	5.69E-03	5.79E-02
Salivary	4.70E-02	5.29E-03	3.60E-03	5.59E-02
Red Marrow	**2.43E-01**	**1.32E-02**	**6.39E-03**	**2.63E-01**
Osteogenic Cells	1.17E+00	2.60E-02	6.11E-03	1.20E+00
Spleen	1.31E-01	1.54E-02	1.38E-02	1.61E-01
Testes	5.91E-02	6.23E-03	3.50E-03	6.87E-02
Thymus	4.70E-02	5.41E-03	5.68E-03	5.80E-02
Thyroid	4.70E-02	5.29E-03	4.78E-03	5.71E-02
Urinary Bladder Wall	4.70E-02	5.29E-03	4.91E-03	5.72E-02
Total Body	8.84E-02	1.02E-02	4.66E-03	1.03E-01