

Supporting Information

**PARP Targeted Auger Therapy in p53 Mutant Colon Cancer
Xenograft Mouse Models**

Figure S1

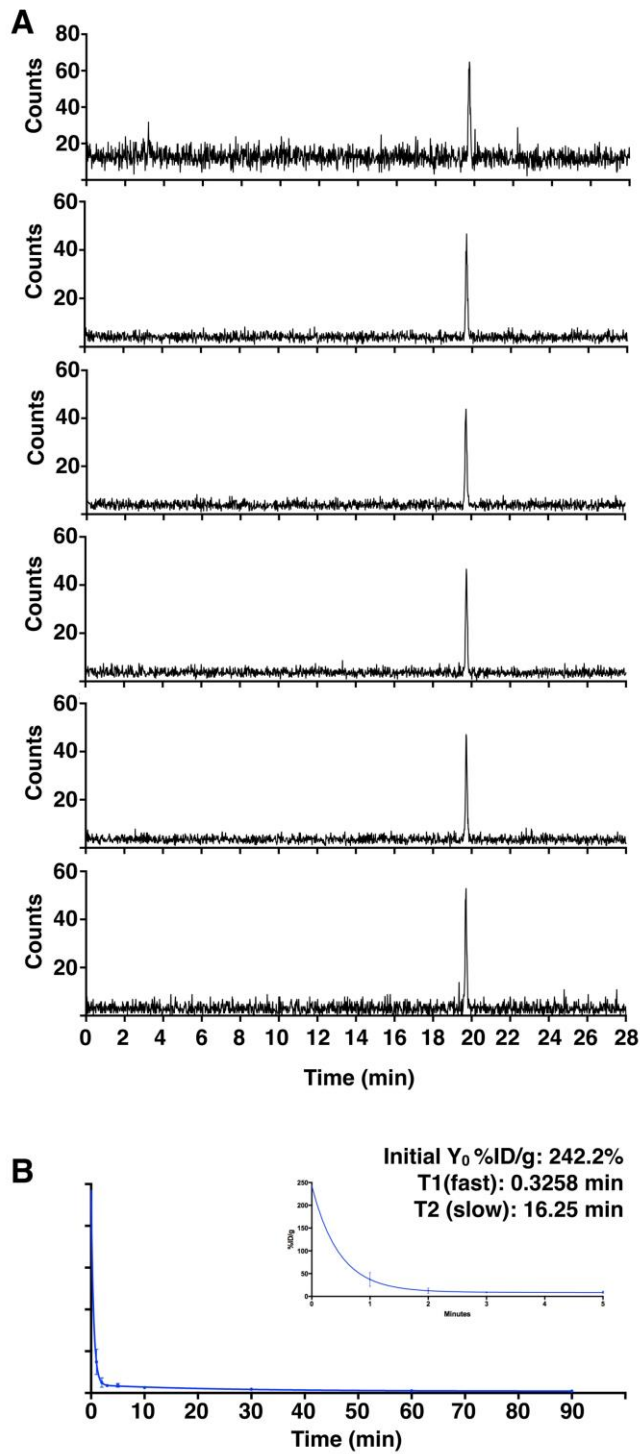


Figure S1. In vitro evaluation of ^{123}I -MAPi serum stability and blood half-life. (A) Stability of ^{123}I -MAPi in 10% FBS serum at 0, 5, 30, 60, 120, 1440 mins time points via Radio-HPLC. **(B)** Blood half-life of ^{123}I -MAPi in healthy nude mice.

Table S1

	D2 Veh M		D15 Veh M		D2 Treat M		D15 Treat M		D2 Veh F		D15 Veh F		Day 2 Treat F		D15 Treat F	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AST (U/L)	72.20	26.85	58.20	19.54	75.80	44.35	83.60	30.91	82.80	21.74	52.20	8.70	118.00	96.45	68.60	12.20
ALT (U/L)	70.80	33.43	67.20	26.49	47.20	26.78	113.40	64.30	39.20	21.53	34.00	13.55	65.40	77.65	31.80	12.99
ALP (U/L)	100.60	43.45	83.80	28.85	93.20	12.77	88.40	28.22	141.00	88.23	100.40	19.68	147.20	53.09	112.00	22.35
GGT (U/L)	2.00	0.00	2.00	0.00	2.00	0.00	2.00	0.00	2.00	0.00	2.00	0.00	2.00	0.00	2.00	0.00
CK (U/L)	700.40	702.45	286.80	197.78	919.20	1598.82	463.00	311.33	464.40	283.80	381.40	276.28	418.40	203.96	313.20	157.69
TBIL (umol/L)	1.30	0.00	2.68	0.85	1.56	0.58	4.68	2.93	1.30	0.00	1.30	0.00	1.30	0.00	1.30	0.00
UREA (nmol/L)	4.88	0.50	5.32	0.58	5.14	0.25	5.32	0.45	5.38	1.48	5.20	0.76	4.74	0.53	4.66	0.43
CREAT (umol/L)	11.00	4.12	8.00	0.00	8.00	0.00	8.00	0.00	11.00	4.12	14.80	4.09	8.00	0.00	8.00	0.00
GLU (nmol/L)	10.97	1.66	9.20	0.63	11.87	1.34	8.90	1.13	11.44	1.52	9.21	1.60	11.55	0.92	9.55	1.52
CHOL (nmol/L)	3.92	0.80	3.96	0.53	9.15	13.11	3.33	0.64	2.24	0.26	2.51	0.48	2.13	0.37	2.46	0.21
TRIG (nmol/L)	0.97	0.35	1.31	0.57	0.97	0.28	1.53	1.06	0.99	0.16	1.17	0.35	1.78	0.64	0.98	0.32
TPROT (g/L)	51.48	3.04	48.14	1.60	49.92	2.48	47.80	2.47	49.32	1.01	49.02	1.85	48.96	2.98	49.90	2.35
ALB (g/L)	33.34	2.10	31.10	0.91	31.42	1.91	28.42	4.40	34.46	1.44	36.02	0.99	34.58	2.88	36.56	1.86
GLOB (g/L)	18.14	1.33	17.04	1.42	18.50	0.84	17.38	1.31	14.86	2.23	13.00	1.40	14.38	1.89	13.34	0.70
A/G Ratio	1.86	0.11	1.82	0.18	1.70	0.10	1.74	0.11	2.36	0.40	2.80	0.31	8.04	12.84	2.76	0.13
Ca (mmol/L)	2.46	0.05	2.41	0.06	2.47	0.06	2.41	0.04	2.43	0.05	2.58	0.16	2.45	0.06	2.44	0.07
Na (mmol/L)	150.80	1.10	149.80	1.48	148.00	1.00	149.00	1.41	149.00	2.24	148.40	2.07	147.80	1.64	149.40	1.67
K (mmol/L)	4.78	0.37	4.58	0.38	4.92	0.30	4.43	0.28	4.08	0.22	3.80	0.34	4.66	0.23	4.00	0.10
Cl (mmol/L)	106.80	2.77	87.80	44.63	105.60	0.55	106.50	1.73	108.00	2.12	108.00	2.24	106.60	2.07	109.00	2.12
Phos (mmol/L)	2.68	0.20	2.13	0.22	2.73	0.38	2.51	0.48	2.60	0.33	2.18	0.43	2.68	0.29	2.19	0.07

Table S1. Complete Toxicity Report of ¹²⁷I-PARPi in healthy mice at 2 days and 15 days post compound administration. Veh: Vehicle; Treat:¹²⁷I-PARPi treated mice at 2.05 mg/kg; D: Day.

Figure S2

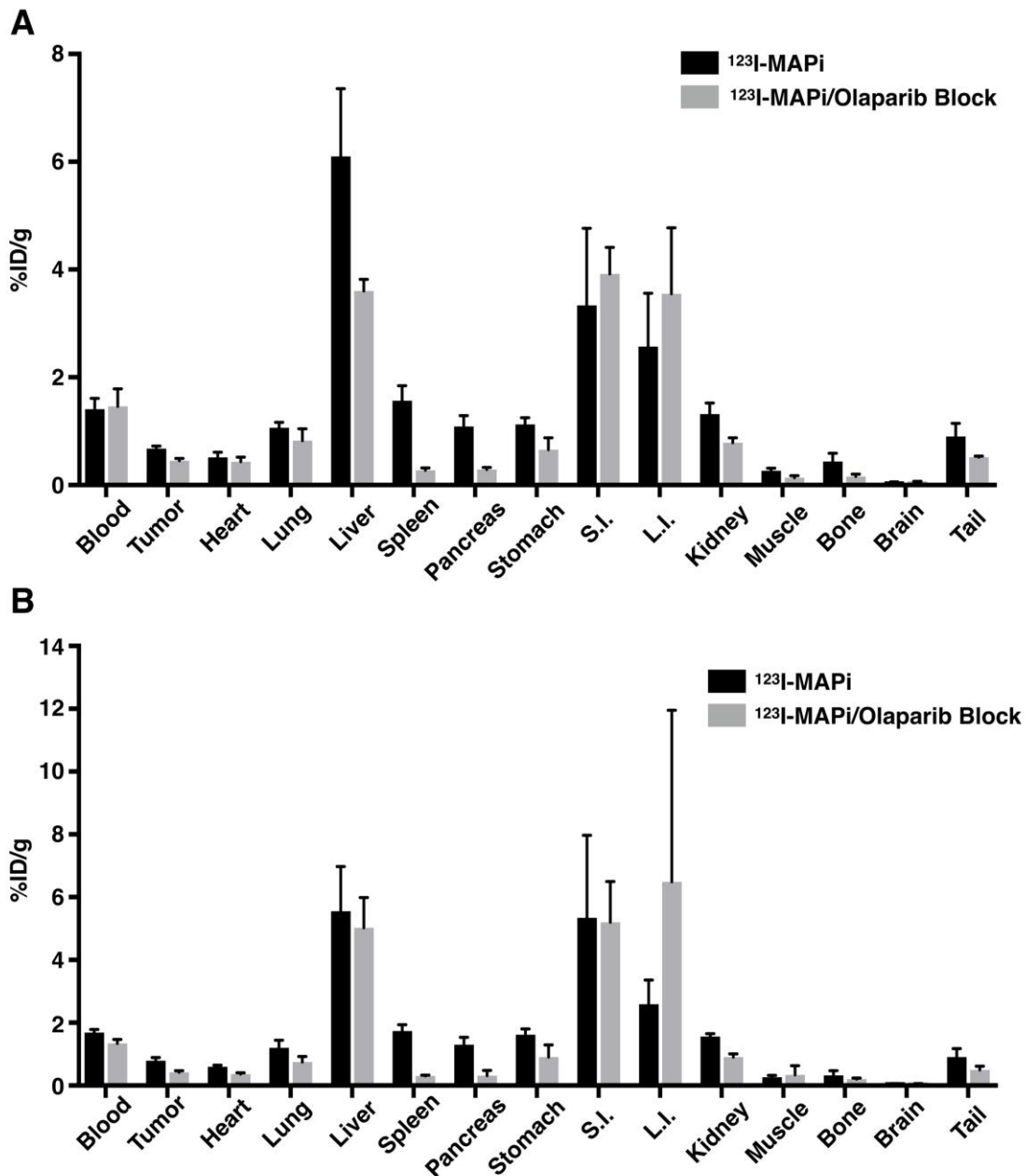


Figure S2. Biodistribution of ^{123}I -MAPi in human colorectal cancer HCT116 p53^{+/+} (A) and HCT116 p53^{-/-} (B) mouse models 1 hour post administration. Animals were treated when implanted tumors were ~100 mm³ size. For blocking, a 1000-fold excess of Olaparib was administered intravenously 1 hour prior to intravenously injection of ^{123}I -MAPi. At 1 hour time point post administration of ^{123}I -MAPi, mice were sacrificed and acute biodistribution studies were carried out.

Table S2

A		¹²³I-MAPi			¹²³I-MAPi /Olaparib Block		
Blood		1.2091	1.3940	1.6171	1.0866	1.6093	1.6866
Tumor		0.6233	0.7164	0.6866	0.4055	0.4583	0.4908
Heart		0.4071	0.5511	0.5848	0.3501	0.4336	0.5217
Lung		0.9695	1.0555	1.1687	0.8728	0.5852	1.0144
Liver		6.0895	4.8405	7.3633	3.5086	3.8517	3.4427
Spleen		1.5275	1.3147	1.8630	0.2263	0.2931	0.3076
Pancreas		0.9104	1.0471	1.3063	0.2461	0.2913	0.3245
Stomach		1.0135	1.1003	1.2618	0.5478	0.5188	0.9084
SI		4.1151	1.6841	4.2073	4.4507	3.8278	3.4800
LI		3.6340	1.6808	2.3940	4.5088	2.1684	3.9714
Kidney		1.1173	1.3034	1.5282	0.6849	0.8133	0.8588
Muscle		0.2086	0.2911	0.2909	0.1269	0.1094	0.1796
Bone		0.2552	0.5397	0.5117	0.1244	0.1502	0.2102
Brain		0.0498	0.0454	0.0590	0.0345	0.0477	0.0688
Tail		0.8088	0.7186	1.1788	0.5051	0.5044	0.5409

B		¹²³I-MAPi			¹²³I-MAPi /Olaparib Block		
Blood		1.7908	1.6018	1.6667	1.4771	1.3287	1.2191
Tumor		0.8524	0.8526	0.6786	0.4349	0.4616	0.3654
Heart		0.6540	0.5514	0.5848	0.4068	0.3712	0.3229
Lung		1.2943	0.9283	1.3799	0.9042	0.7806	0.5649
Liver		6.5471	3.9199	6.1782	5.7902	3.9461	5.3489
Spleen		1.8844	1.5066	1.8136	0.3131	0.3212	0.2789
Pancreas		1.2013	1.1407	1.5683	0.4880	0.3075	0.1479
Stomach		1.8089	1.4524	1.6034	1.0497	1.2030	0.4728
SI		2.4670	5.9398	7.6217	3.7147	5.7827	6.1045
LI		3.4051	2.4935	1.8646	12.7054	4.3060	2.4479
Kidney		1.5454	1.4841	1.6631	1.0057	0.9151	0.8008
Muscle		0.2276	0.2474	0.3249	0.2222	0.1331	0.6729
Bone		0.4417	0.3729	0.1577	0.2401	0.1857	0.1795
Brain		0.0555	0.0652	0.0632	0.0608	0.0555	0.0431
Tail		1.0911	0.6057	1.0282	0.6161	0.4951	0.3884

Table S2. Bio-distribution tables for ¹²³I-MAPi in selected cell lines expressed as %ID/g. The values reported are at 1 hour post administration of ¹²³I-MAPi. For blocking doses, a 1000-fold excess of Olaparib was injected 1 hour prior to administration of ¹²³I-MAPi A) HCT116 p53^{+/+}; B) HCT116 p53^{-/-}.

Figure S3

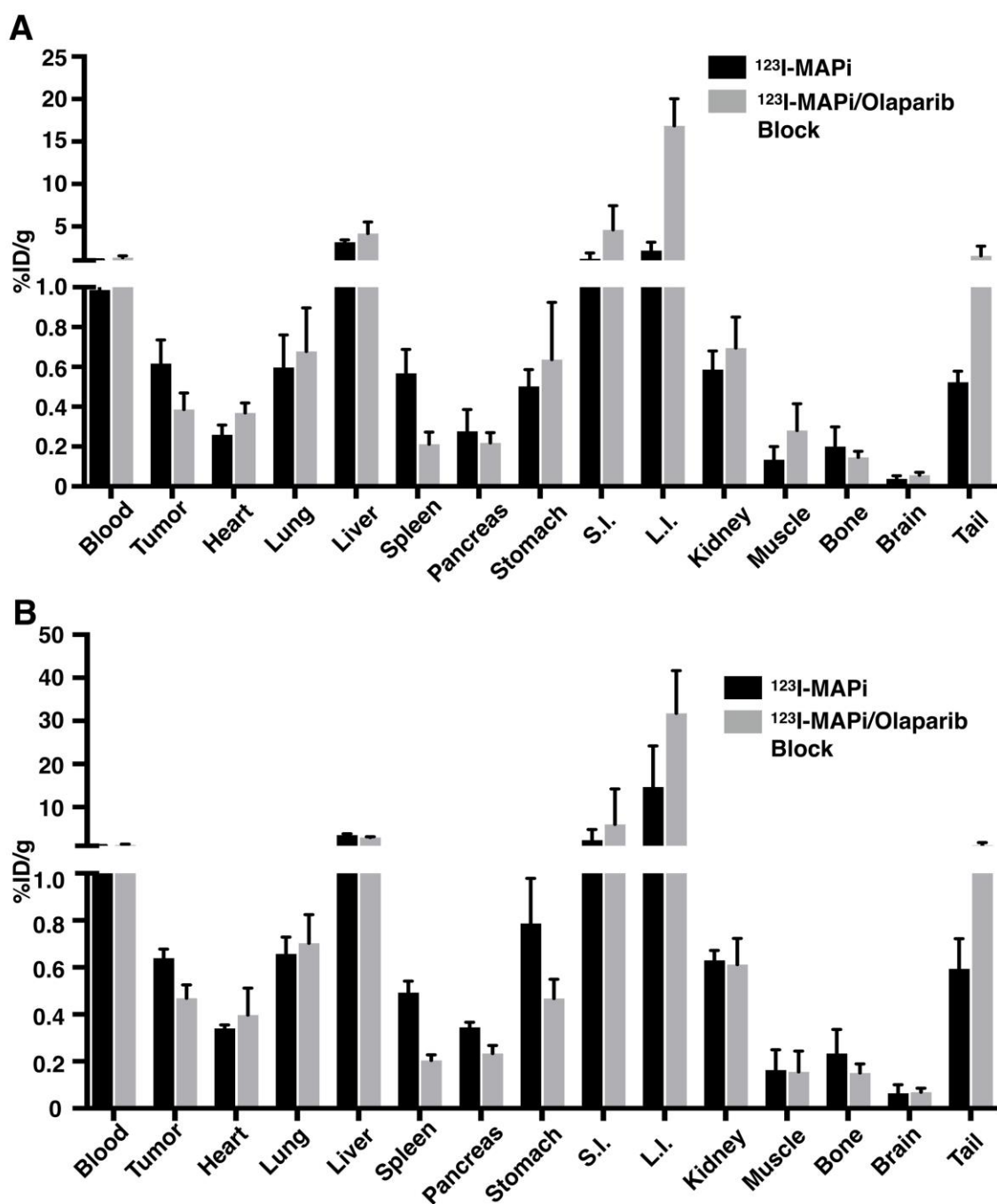


Figure S3. Biodistribution of ^{123}I -MAPi in human colorectal cancer (A) HCT116 p53^{+/+} and (B) HCT116 p53^{-/-} mouse models 2 hours post administration. Animals were treated when implanted tumors were ~100 mm³ size. For blocking, a 1000-fold excess Olaparib was administered intravenously 1 hour prior to intravenously injection of ^{123}I -MAPi. At 2-hour time point post administration of ^{123}I -MAPi, mice were sacrificed and acute biodistribution studies carried out.

Table S3**A**

	¹²³ I-MAPi			¹²³ I-MAPi/Olaparib Block		
Blood	0.8712	1.0531	1.0358	1.0795	1.3765	1.4920
Tumor	0.5103	0.5920	0.7462	0.2966	0.3964	0.4634
Heart	0.2195	0.2421	0.3145	0.3131	0.3858	0.4079
Lung	0.4173	0.6379	0.7371	0.4244	0.8032	0.8036
Liver	2.9662	2.9940	3.4830	3.9109	2.9619	5.6420
Spleen	0.4290	0.6227	0.6506	0.1482	0.2168	0.2691
Pancreas	0.1848	0.3973	0.2460	0.1596	0.2352	0.2598
Stomach	0.4589	0.4478	0.5998	0.3228	0.8874	0.7006
SI	0.5605	1.9073	1.1094	3.1649	2.7170	7.8900
LI	1.0840	3.0538	2.3576	16.8327	20.0430	13.7128
Kidney	0.4795	0.6531	0.6269	0.5619	0.6575	0.8660
Muscle	0.2083	0.1102	0.0817	0.3706	0.1255	0.3438
Bone	0.0938	0.2900	0.2146	0.1186	0.1432	0.1773
Brain	0.0194	0.0506	0.0412	0.0424	0.0530	0.0723
Tail	0.5138	0.5831	0.4736	0.8678	0.9083	2.8453

B

	¹²³ I-MAPi			¹²³ I-MAPi/Olaparib Block		
Blood	1.1004	1.0121	1.0123	1.0717	1.1335	1.4296
Tumor	0.6146	0.6208	0.6835	0.4420	0.4292	0.5345
Heart	0.3404	0.3265	0.3556	0.3419	0.3202	0.5286
Lung	0.6021	0.7387	0.6325	0.5887	0.6897	0.8311
Liver	3.6451	3.7099	3.1251	2.8951	2.7917	3.1608
Spleen	0.4395	0.5023	0.5351	0.1946	0.1862	0.2312
Pancreas	0.3534	0.3618	0.3210	0.2084	0.2180	0.2727
Stomach	0.8854	0.9099	0.5656	0.4659	0.5501	0.3853
SI	5.1336	0.5365	1.4126	1.2278	1.2788	15.5024
LI	15.9482	4.5189	23.4676	40.3057	20.8862	34.0345
Kidney	0.6785	0.6058	0.6069	0.5174	0.5842	0.7343
Muscle	0.2622	0.1112	0.1160	0.0793	0.2519	0.1344
Bone	0.3512	0.1772	0.1722	0.1189	0.1410	0.1926
Brain	0.1044	0.0538	0.0359	0.0550	0.0646	0.0877
Tail	0.6389	0.6941	0.4497	0.6382	1.8537	0.9909

Table S3. Bio-distribution tables for ¹²³I-MAPi in selected cell lines expressed as %ID/g. The values reported are at 2-hour post administration of ¹²³I-MAPi. For blocking doses, a 1000-fold excess of Olaparib was injected 1 hour prior to administration of ¹²³I-MAPi A) HCT116 p53^{+/+}; B) HCT116 p53^{-/-}.

Table S4

	Blood	Heart	Lungs	Liver	Spleen	Pancreas	Stomach	SI	LI	Kidney	Muscle	Bone	Skin	Brain	Thyroid	Tail
1Hr	0.7450	0.5404	1.1869	6.0143	1.8582	1.0658	1.9038	3.7463	1.0700	1.3800	0.2731	0.8953	0.7235	0.2047	10.5948	0.6188
	1.2346	0.4845	0.7615	5.7361	1.4992	0.7153	1.0303	4.0654	0.5836	0.8388	0.3950	0.6302	1.0055	0.0662	4.5140	4.2079
	1.9542	0.8865	1.5766	8.6314	1.9973	1.8237	2.4565	2.0768	1.2960	1.8073	0.9805	1.2229	1.2092	0.0995	6.0327	1.3386
6Hr	0.2352	0.0990	0.6195	1.4511	0.0804	0.0570	0.1589	0.1915	0.3155	0.1212	0.0302	0.0316	0.1030	0.0055	0.0570	0.2960
	0.3208	0.0883	1.1556	1.3561	0.1041	0.0998	0.1721	0.3023	0.6827	0.1387	0.0290	0.0560	0.1080	0.1446	0.0725	0.2377
	0.6944	0.2615	0.7276	1.1969	0.1338	0.1265	0.2924	0.2930	0.7559	0.2906	0.0579	0.0596	0.2111	0.0248	0.1414	0.3614
15Hr	0.0805	0.0160	0.0324	0.4665	0.0157	0.0139	0.0935	0.0789	0.0929	0.0476	0.0054	0.0079	0.0446	0.0018	0.0128	0.0555
	0.0879	0.0212	0.0844	0.5821	0.0234	0.0160	0.0667	0.0672	0.0706	0.0514	0.0239	0.0091	0.0562	0.0024	3.6231	0.1246
	0.0648	0.0208	0.0406	0.4915	0.0185	0.0300	0.0408	0.0841	0.1563	0.0437	0.0076	0.0061	0.0376	0.0024	0.0204	0.1089
24Hr	0.0153	0.0051	0.0964	0.1444	0.0064	0.0037	0.0116	0.0134	0.0255	0.0095	0.0010	0.0050	0.0086	0.0002	0.0051	0.0214
	0.0147	0.0056	0.0146	0.1549	0.0036	0.0039	0.0300	0.0184	0.0819	0.0108	0.0003	0.0000	0.0097	0.0003	0.0000	0.3483
	0.0104	0.0149	0.8216	0.0007	0.0464	0.0670	0.2311	0.3343	0.0059	0.0027	0.0031	0.3826	0.0000	0.0058	3.9427	0.0000
48Hr	0.0061	0.0023	0.0032	0.0833	0.0025	0.0010	0.0102	0.0046	0.0111	0.0063	0.0011	0.0000	0.0046	0.0006	0.0145	0.1397
	0.0064	0.0037	-0.0003	0.0840	0.0024	0.0041	0.0037	0.0020	0.0062	0.0062	0.0017	0.0013	0.0040	0.0000	0.0014	0.0277
	0.0088	0.0024	0.0042	0.1015	0.0006	0.0017	0.0081	0.0020	0.0039	0.0087	0.0000	0.0000	0.0089	0.0000	1.7667	0.0594

Table S4. Bio-distribution of ¹²³I-MAPi in healthy athymic nude mice. All numbers expressed as %ID/g

Table S5

Tissue	¹²³ I-MAPI	
	Absorbed Dose (rad/mCi)	
	<i>Mouse</i>	<i>Human</i>
Adrenals		0.00556
Brain	0.124	0.00124
Breasts		0.00285
Gallbladder Wall		0.00800
Lower Large Intestine Wall	1.72	0.0295
Small Intestine	3.29	0.01320
Stomach Wall	1.90	0.00503
Upper Large Intestine Wall	1.72	0.01100
Heart Wall	2.15	0.00449
Kidneys	2.68	0.00598
Liver	16.3	0.0154
Lungs	5.94	0.00587
Muscle	1.00	0.00916
Ovaries		0.00261
Pancreas	1.63	0.00543
Red Marrow		0.00704
Bone	2.12	0.00229
Skin	2.08	0.00390
Spleen	3.06	0.00461
Testes		0.01830
Thymus		0.00354
Thyroid	15.0	0.00906
Urinary Bladder Wall - 4-hr Voiding Interval		0.652
Uterus		0.0614
Total Body		0.00950
Effective Dose (rem/mCi)		0.0458

Table S5. Dosimetry Data for ¹²³I-MAPI in healthy athymic nude mice and the equivalent dose in humans

Table S6

	Vehicle		24 hours		1 week		2 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BUN (mg/dL)	23.00	5.29	26.00	4.58	23.33	4.62	28.00	1.00
CREA (mg/dL)	0.17	0.04	0.26	0.04	0.20	0.08	0.20	0.02
BUN/CREA Ratio	132.93	2.41	100.43	16.96	116.30	17.39	143.23	16.49
ALP (U/L)	73.00	2.00	82.67	4.93	79.67	1.53	81.67	7.23
ALT (U/L)	30.00	3.61	32.00	7.00	36.33	4.62	51.33	43.09
AST (U/L)	64.67	1.15	64.33	15.82	78.33	19.04	131.67	125.01
GGT (U/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
TBIL (mg/dL)	0.10	0.00	0.20	0.00	0.10	0.00	0.10	0.00
DBIL (mg/dL)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
IBIL (mg/dL)	0.10	0.00	0.20	0.00	0.10	0.00	0.10	0.00
TP (g/dL)]	5.20	0.46	5.03	0.25	4.77	0.21	5.03	0.35
ALB (g/dL)	3.03	0.25	3.07	0.21	2.97	0.12	2.97	0.06
GLOB (g/dL)	2.17	0.21	1.97	0.06	1.80	0.10	2.07	0.31
A/G Ratio	1.40	0.00	1.53	0.06	1.63	0.06	1.47	0.15
P (mg/dL)	5.43	0.59	6.50	0.96	6.65	0.21	5.97	1.01
Ca (mg/dL)	9.27	0.64	10.10	0.56	9.45	0.64	9.50	0.44
GLU (mg/dL)	247.67	40.50	249.33	41.55	267.50	3.54	208.67	13.32
CHOL (mg/dL)	80.67	7.02	90.67	2.52	84.00	1.41	76.00	4.00
TRIG(mg/dL)	85.67	38.18	87.67	7.51	83.00	1.41	90.33	18.01
CK (U/L)	166.67	77.39	223.67	150.04	270.00	178.47	101.33	83.77
TCO2 (mEq/L)	17.33	1.53	19.67	2.08	15.50	2.12	16.67	0.58
Na (mEq/L)	154.67	8.33	166.33	10.50	154.00	5.66	163.33	5.03
K (mEq/L)	3.93	0.49	4.67	0.81	4.70	0.28	3.73	0.50
CL (mEq/L)	114.00	4.36	119.33	7.02	112.50	3.54	119.33	3.06
Na/K	40.00	6.56	36.33	4.04	33.00	2.83	44.33	6.51
Anion Gap	27.67	2.08	32.00	2.65	31.00	4.24	31.00	2.00

Table S6. Complete Toxicity Report of ¹²³I-MAPi in healthy mice at 24 hours, 7 days, 14 days. 24 hour cohort, 1 week cohort and 2 weeks cohorts refer to the time between administration of ¹²³I-MAPi and time of sacrifice for analysis.

Figure S4

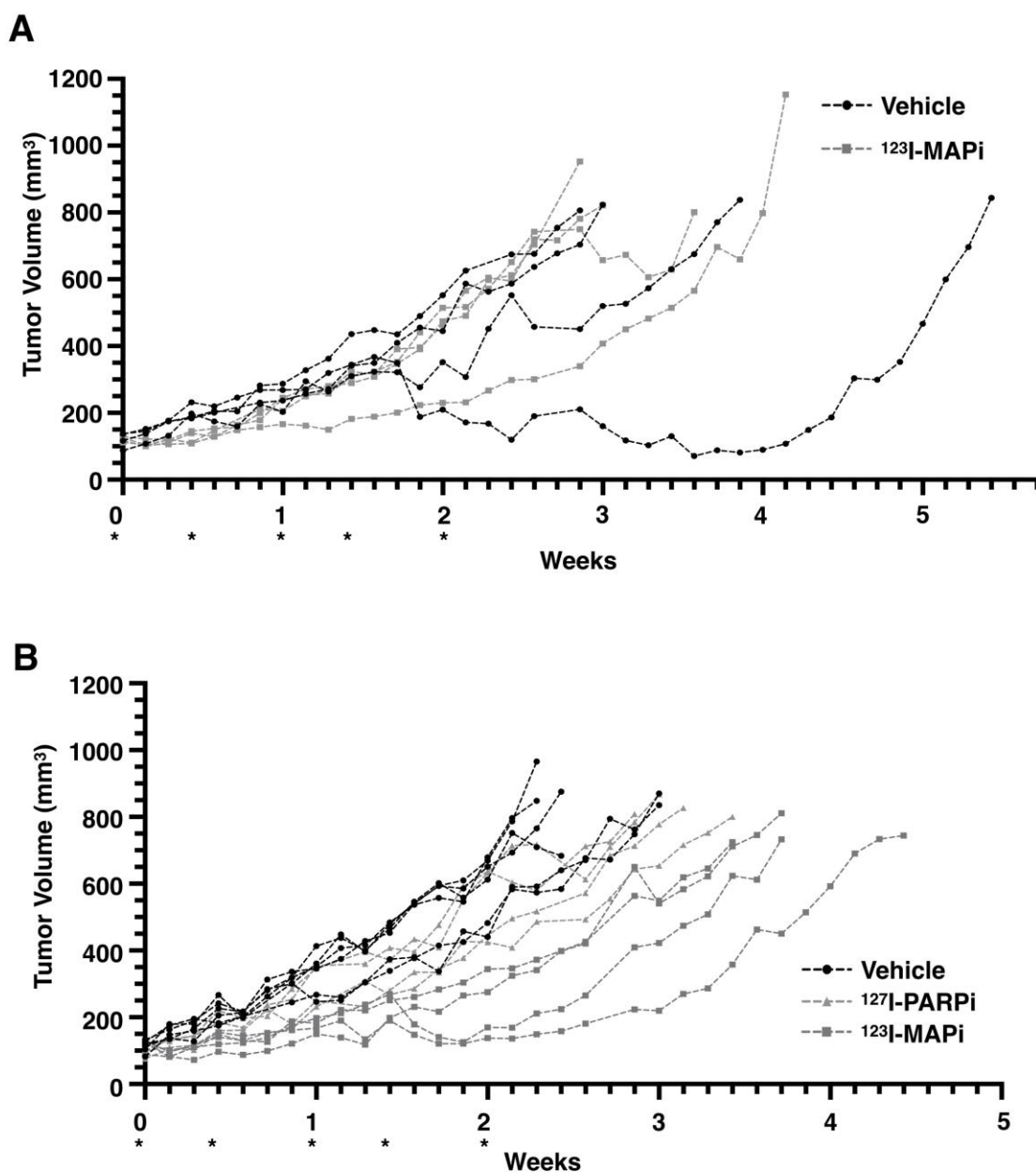


Figure S4. Tumor growth curves of either HCT116 p53^{+/+} or HCT116 p53^{-/-} mouse models when treated with vehicle, ¹²⁷I-PARPi or ¹²³I-MAPi. (A) HCT116 p53^{+/+} bearing mice treated intravenously with vehicle or 123I-MAPi at days 0, 3, 7, 10, 14. (B) HCT116 p53^{-/-} bearing mice treated intravenously with vehicle, ¹²⁷I-PARPi or ¹²³I-MAPi at days 0, 3, 7, 10, 14. Athymic nude mice bearing tumors were treated every 3-4 days with either vehicle, ¹²⁷I-PARPi or ¹²³I-MAPi for 5 cycles of treatment with daily tumor volume measurements taken. *Represents day of treatment.

Figure S5

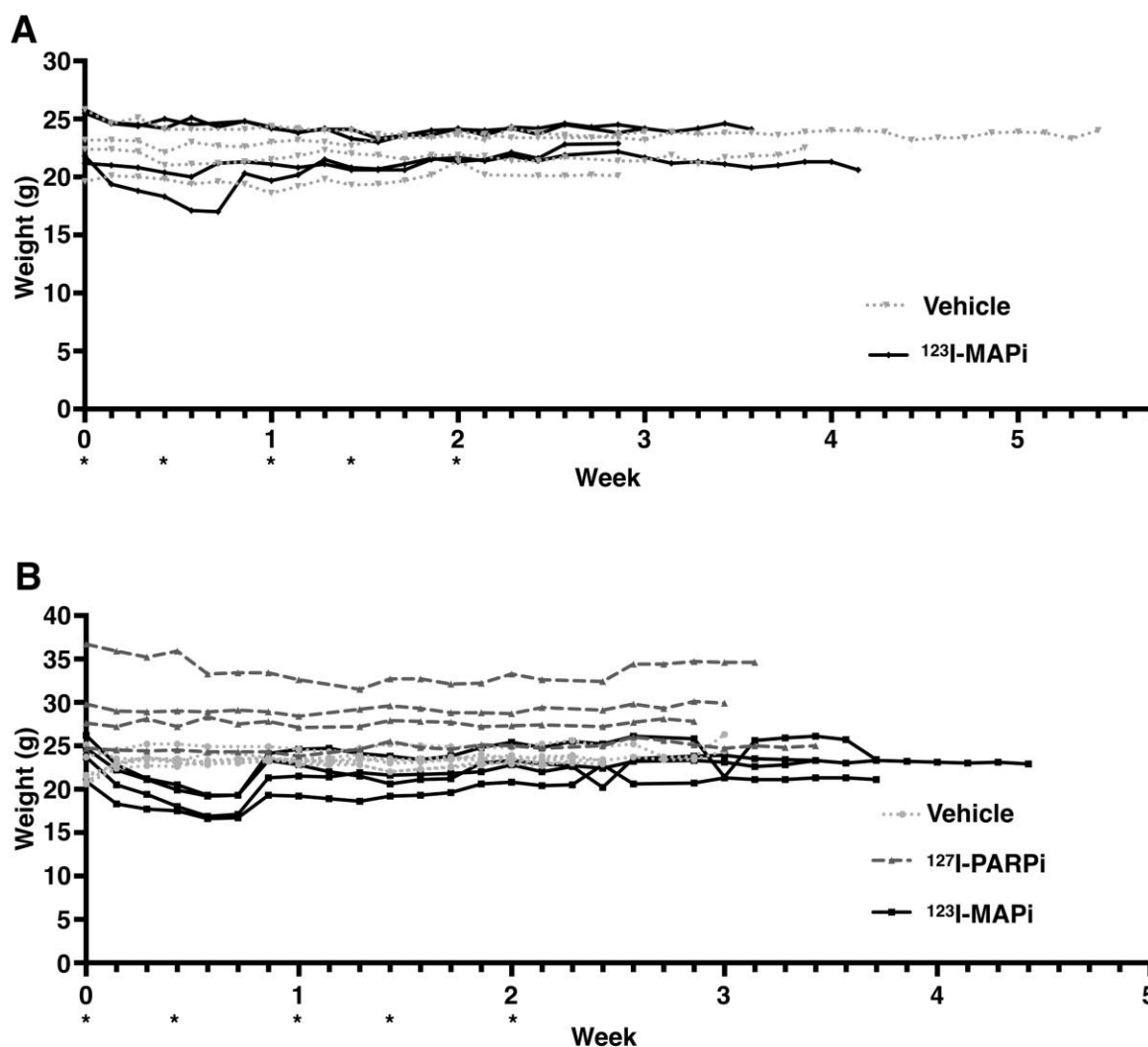


Figure S5. Weights of mice of either HCT116 p53^{+/+} or HCT116 p53^{-/-} mouse models when treated with vehicle, $^{127}\text{I-PARPi}$ or $^{123}\text{I-MAPi}$. (A) HCT116 p53^{+/+} bearing mice treated intravenously with vehicle or $^{123}\text{I-MAPi}$ at days 0, 3, 7, 10, 14; (B) HCT116 p53^{-/-} bearing mice treated intravenously with vehicle, $^{127}\text{I-PARPi}$ or $^{123}\text{I-MAPi}$ at days 0, 3, 7, 10, 14. Athymic nude mice bearing tumors were treated every 3-4 days with either vehicle, $^{127}\text{I-PARPi}$ or $^{123}\text{I-MAPi}$ for 5 cycles of treatment with daily body weight measurements taken. *Represents day of treatment.