

Supplementary information

Development of a drug-device combination for fluorescence-guided surgery in neuroendocrine tumors

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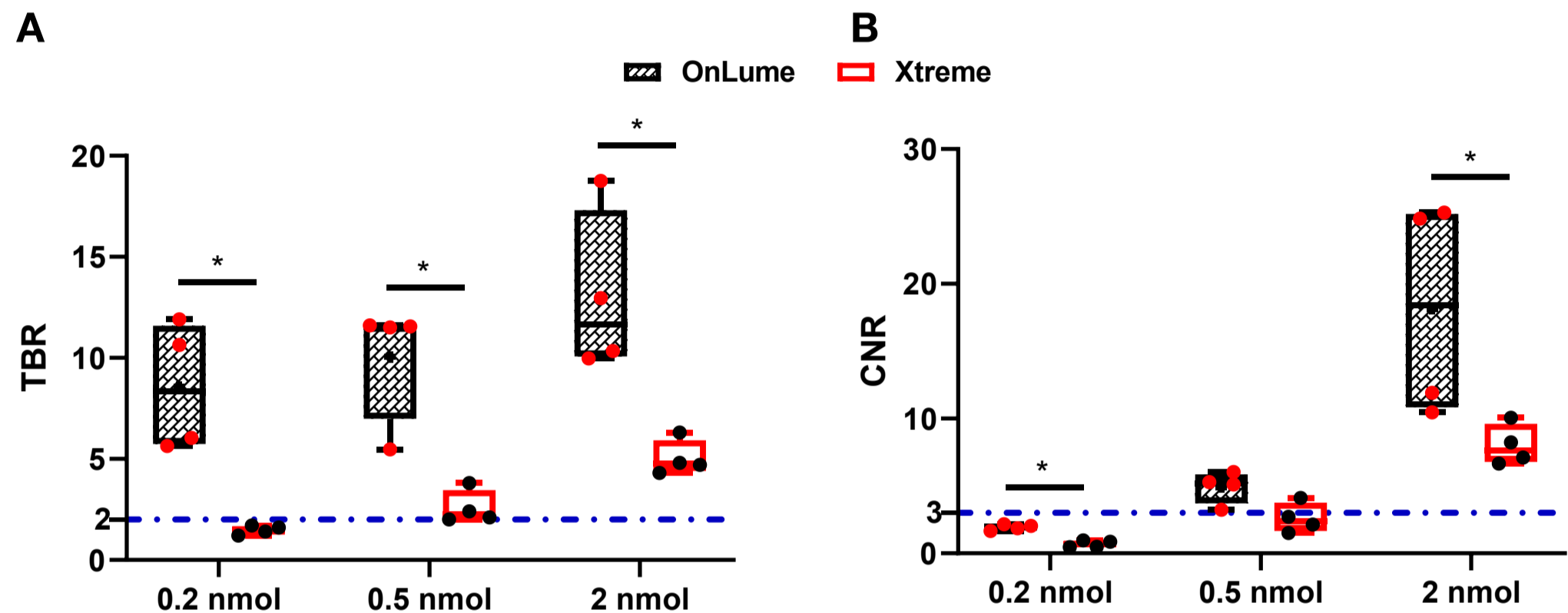
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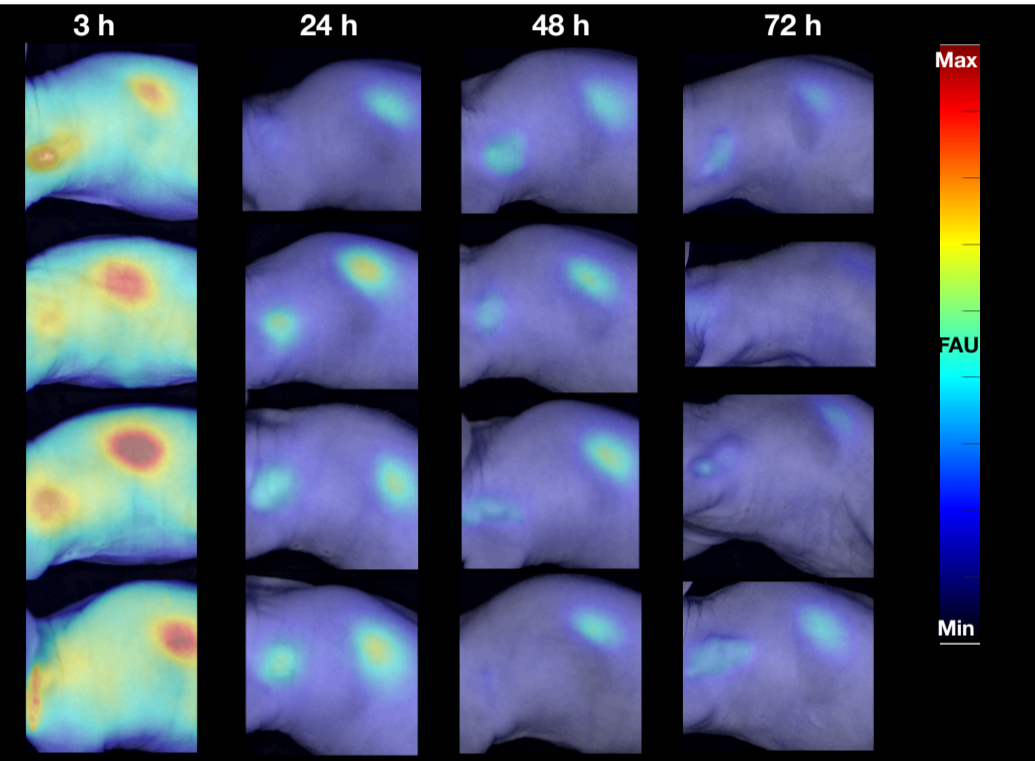
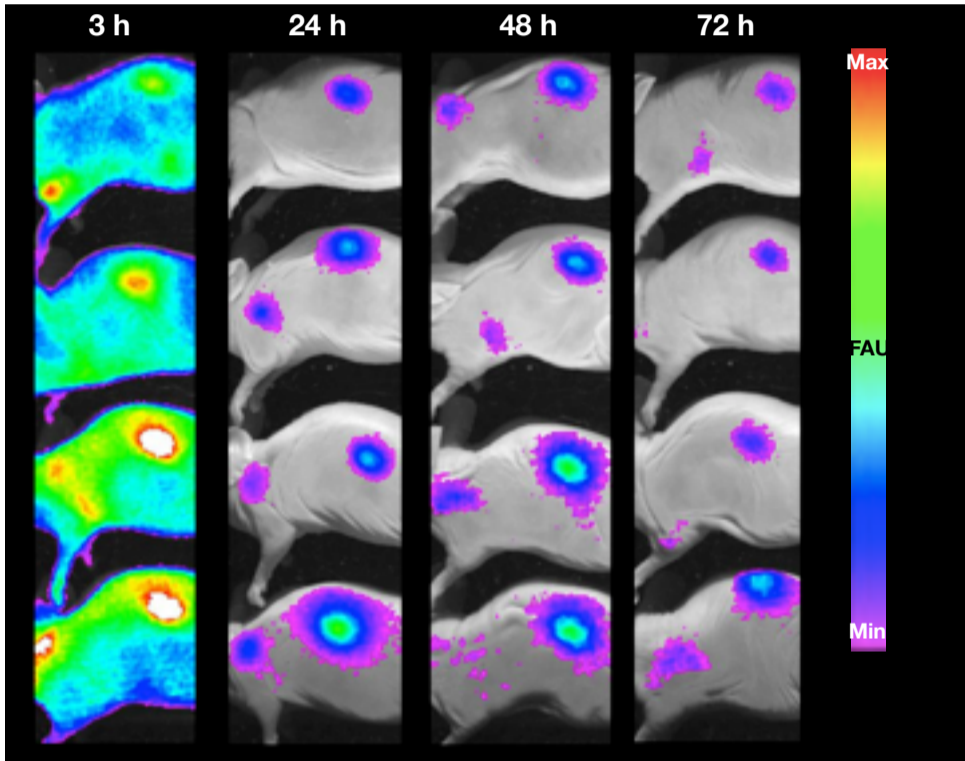
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Running title: Drug-device combination for FGS in NETs



Supplementary Figure 1. Comparison of tumor contrast on the OnLume imager and In-Vivo Xtreme (preclinical small animal imaging device) as a function of ^{67}Ga -MMC(IR800)-TOC dose. Mice with HCT116-SSTR2 tumors were intravenously injected with 0.2, 0.5 or 2 nmol of drug. 24 hours post-injection mice were sacrificed and tumor, muscle were excised and imaged with the OnLume imager and In-Vivo Xtreme (Bruker) to determine (A) TBR and (B) CNR. The dashed-dotted blue lines in (A) and (B) represent the commonly used threshold for TBR and the Rose criterion, respectively. The box plot extends from the 25th to 75th percentiles, the line in the middle indicates the median, the cross indicates the mean, and the whiskers extend from the minimum to the maximum value ($n = 4/\text{dose}$). *, $P < 0.05$.

A**B**

Supplementary Figure 2. *In vivo* time-course fluorescence imaging of mouse cohorts injected with optimal dose. Mice with HCT116-SSTR2 tumors were intravenously injected with 2 nmol of drug and imaged longitudinally over time using the (A) OnLume imager and (B) In-Vivo Xtreme (n = 4/time point).

Supplementary Table 1. Fluorescence arbitrary units (FAUs) for 2 nmol of ⁶⁷Ga-MMC(IR800)-TOC in HCT116-SSTR2 xenografts at 3, 24, 48 and 72 h post-injection (n = 4/time point). S.I., small intestine.

	3 h	24 h	48 h	72 h
Tumor	302.3 ± 102.7	369.7 ± 156.1	174.9 ± 51.8	175.4 ± 27.7
Muscle	40.8 ± 4.4	28.3 ± 8.9	34.5 ± 5.2	36.5 ± 4.7
Pancreas	163.9 ± 17.9	125.7 ± 38.1	80.2 ± 11.2	97.7 ± 15.4
S. I.	51.0 ± 8.7	41.7 ± 6.6	39.3 ± 1.5	39.6 ± 5.7
Lung	373.2 ± 75.8	159.5 ± 27.5	82.2 ± 20.2	66.1 ± 9.9
Liver	329.6 ± 30.6	266.4 ± 23.0	196.7 ± 29.3	158.9 ± 37.2
Spleen	103.8 ± 18.0	55.8 ± 11.4	54.4 ± 6.2	46.7 ± 5.9
Stomach	169.0 ± 56.5	135.9 ± 38.9	101.4 ± 12.8	113.5 ± 38.9
Bone	213.9 ± 45.9	103.8 ± 25.8	75.4 ± 9.1	64.9 ± 6.7
Heart	116.6 ± 56.7	53.5 ± 19.6	48.8 ± 10.0	46.7 ± 8.8
Adrenal	57.4 ± 7.0	40.5 ± 10.6	46.8 ± 6.4	46.7 ± 1.4
Kidney	1641.4 ± 105.9	1704.7 ± 178.5	809.8 ± 186.5	729.3 ± 36.2
Brain	27.0 ± 9.5	27.0 ± 8.3	38.7 ± 3.4	37.7 ± 3.3
Skin	429.6 ± 85.0	203.2 ± 50.9	103.6 ± 14.7	108.5 ± 14.5

Supplementary Table 2. Fluorescence arbitrary units (FAUs) for 0.2, 0.5 and 2 nmol of ⁶⁷Ga-MMC(IR800)-TOC in HCT116-SSTR2 xenografts at 24 h post-injection (n = 4/time point). S.I., small intestine.

	0.2 nmol	0.5 nmol	2 nmol
Tumor	35.5 ± 2.8	88.9 ± 18.3	369.7 ± 156.1
Muscle	4.3 ± 5.5	9.2 ± 1.7	28.3 ± 8.9
Pancreas	16.0 ± 1.6	36.1 ± 9.3	125.7 ± 38.1
S. I.	10.0 ± 4.8	14.2 ± 2.4	41.7 ± 6.6
Lung	12.3 ± 6.5	37.0 ± 9.3	159.5 ± 27.5
Liver	31.2 ± 9.2	77.9 ± 21.0	266.4 ± 23.0
Spleen	8.9 ± 5.0	13.4 ± 6.9	55.8 ± 11.4
Stomach	18.0 ± 6.3	37.6 ± 8.7	135.9 ± 38.9
Bone	18.3 ± 8.6	36.2 ± 3.8	103.8 ± 25.8
Heart	8.1 ± 6.8	19.5 ± 2.7	53.5 ± 19.6
Adrenal	15.1 ± 4.8	16.5 ± 2.8	40.5 ± 10.6
Kidney	126.1 ± 23.7	412.00 ± 52.9	1704.7 ± 178.5
Brain	18.1 ± 2.7	18.7 ± 3.0	27.0 ± 8.3
Skin	32.3 ± 1.3	65.1 ± 5.3	369.7 ± 156.1

Supplementary Table 3. Biodistribution results (%ID/g) for 0.2, 0.5 and 2 nmol of ⁶⁷Ga-MMC(IR800)-TOC in HCT116-SSTR2 xenografts at 24 h post-injection (n = 4/time point). S.I., small intestine.

	0.2 nmol	0.5 nmol	2 nmol
Tumor	3.75 ± 0.98	6.48 ± 1.87	9.69 ± 2.50
Muscle	0.28 ± 0.27	0.31 ± 0.04	0.62 ± 0.27
Pancreas	1.24 ± 0.14	2.20 ± 0.85	2.98 ± 0.87
S. I.	0.82 ± 0.60	1.01 ± 0.49	2.89 ± 2.24
Lung	1.71 ± 0.57	3.03 ± 0.64	6.89 ± 0.94
Liver	2.96 ± 0.87	6.11 ± 0.69	8.14 ± 1.26
Spleen	1.20 ± 0.16	2.53 ± 1.36	3.66 ± 0.58
Stomach	1.81 ± 0.83	3.55 ± 1.78	5.62 ± 2.14
Bone	0.73 ± 0.14	1.40 ± 0.31	1.96 ± 0.42
Heart	0.34 ± 0.08	0.69 ± 0.10	1.04 ± 0.18
Adrenal	0.92 ± 0.20	3.54 ± 3.16	2.50 ± 0.90
Kidney	17.17 ± 3.53	28.00 ± 4.08	46.75 ± 5.28
Brain	0.02 ± 0.0	0.03 ± 0.01	0.12 ± 0.14
Blood	0.17 ± 0.04	0.27 ± 0.04	0.44 ± 0.12
Skin	1.10 ± 0.26	1.98 ± 0.13	2.45 ± 0.17

Supplementary Table 4. Biodistribution results (%ID/g) for 2 nmol of ⁶⁷Ga-MMC(IR800)-TOC in HCT116-SSTR2 xenografts at 3, 24, 48 and 72 h post-injection (n = 4/time point). S.I., small intestine.

	3 h	24 h	48 h	72 h
Tumor	6.26 ± 2.28	9.69 ± 2.50	8.40 ± 1.24	4.28 ± 0.84
Muscle	1.05 ± 0.17	0.62 ± 0.27	0.41 ± 0.33	0.22 ± 0.04
Pancreas	2.50 ± 0.66	2.98 ± 0.87	1.72 ± 0.52	1.84 ± 0.45
S. I.	1.92 ± 0.82	2.89 ± 2.24	1.19 ± 0.44	0.51 ± 0.06
Lung	14.99 ± 0.35	6.89 ± 0.94	2.27 ± 0.30	1.21 ± 0.30
Liver	7.03 ± 0.91	8.14 ± 1.26	5.52 ± 0.80	3.74 ± 0.49
Spleen	5.57 ± 0.99	3.66 ± 0.58	2.05 ± 0.35	1.56 ± 0.26
Stomach	5.38 ± 1.21	5.62 ± 2.14	2.28 ± 0.49	1.53 ± 0.79
Bone	3.24 ± 0.80	1.96 ± 0.42	1.21 ± 0.24	0.98 ± 0.15
Heart	1.90 ± 0.40	1.04 ± 0.18	0.52 ± 0.13	0.42 ± 0.09
Adrenal	2.78 ± 0.65	2.50 ± 0.90	1.51 ± 1.26	1.08 ± 0.22
Kidney	42.82 ± 3.13	46.75 ± 5.28	29.20 ± 4.14	21.99 ± 1.54
Brain	0.05 ± 0.01	0.12 ± 0.14	0.02 ± 0.01	0.02 ± 0.01
Blood	1.04 ± 0.50	0.44 ± 0.12	0.18 ± 0.04	0.13 ± 0.03
Skin	4.92 ± 1.90	2.45 ± 0.17	1.36 ± 0.58	1.19 ± 0.20