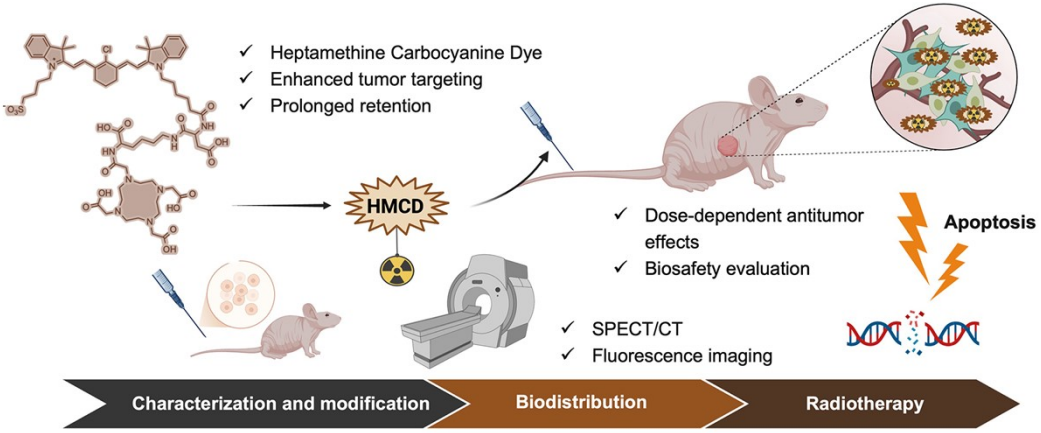



**Table of Contents Entry**

# Results

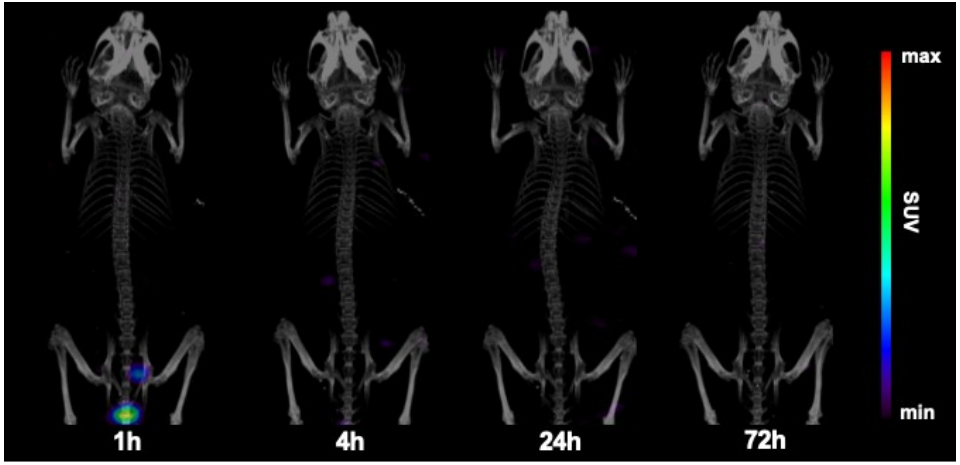
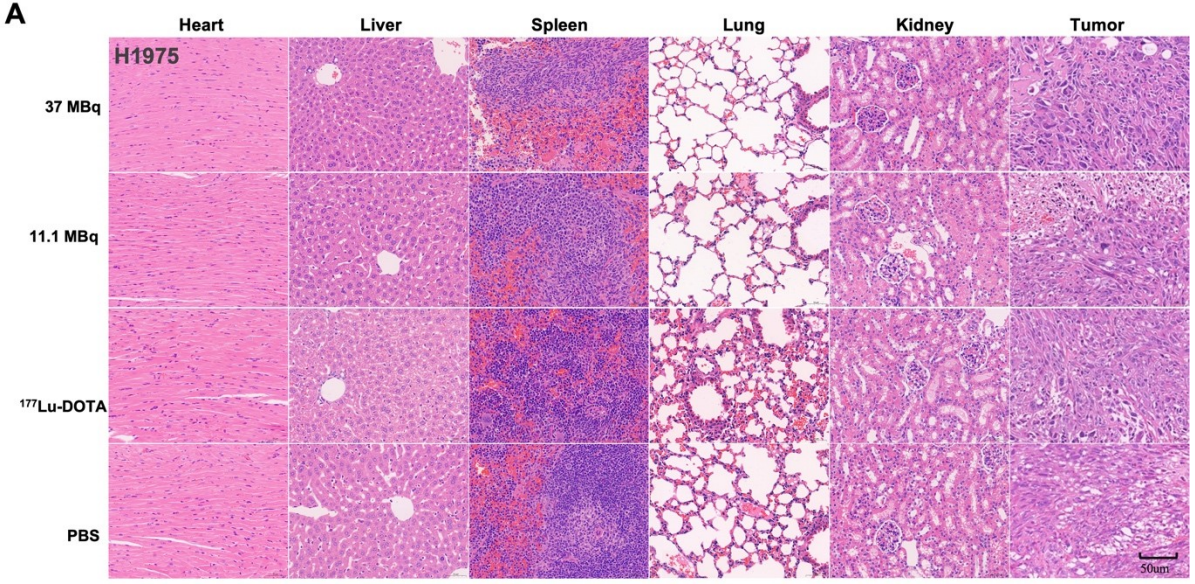



**Figure S1.** SPECT imaging of [$^{177}$Lu]Lu-DOTA on H1975 xenograft models.


A
Heart
Liver
Spleen
Lung
Kidney
Tumor
H1975
37 MBq
11.1 MBq
177Lu-DOTA
PBS
50um

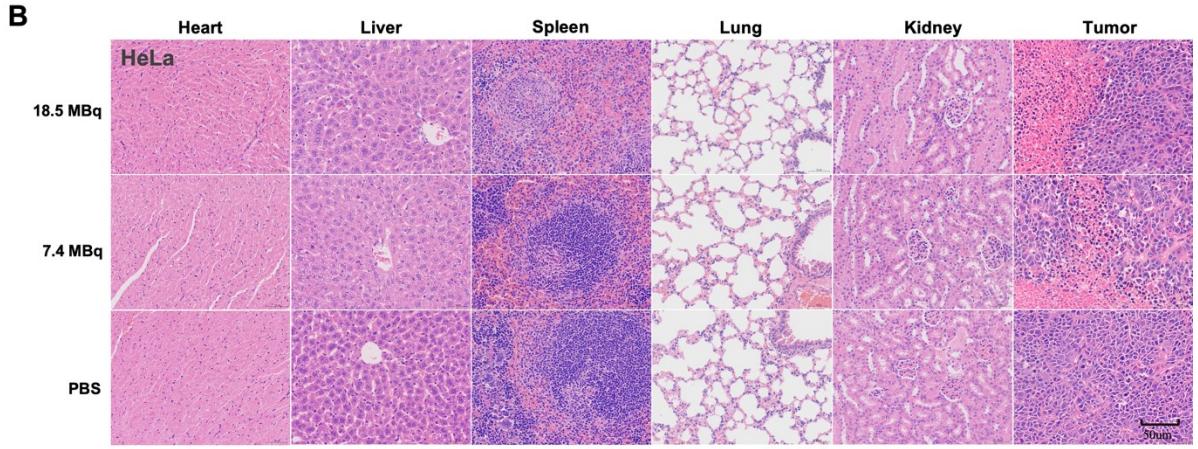



**Figure S2.** H&E staining was performed on major organs (heart, lung, liver, spleen, and kidney) and tumors for H1975 (A) and HeLa (B) xenograft models. Scale bar: 50 μm.

***Animal SPECT image acquisition and processing***

**Table S1** summarizes the performance metrics of the animal SPECT scanner.

**Table S2** provides detailed information on animal SPECT image acquisition and processing parameters.

**Table S1. Characteristics of the Novel Medical animal SPECT scanner**

| Imaging module | Performance metrics | |
|---|---|---|
| **SPECT** | Cross-sectional view | 70 mm |
| | Axial effective field of view | 250 mm |
| | Spatial resolution | ≤ 1.5 mm |
| | Central detection efficiency | ≥ 0.4%（Tc99m） |
| | Energy Range | 80 kev–400 kev |
| | Image Uniformity | < 15% |
| **CT** | Maximum cross-sectional field of view | 70 mm |
| | Maximum axial field of view | 250 mm |
| | High contrast resolution | ≥ 6.25 lp/mm |
| | Low contrast resolution | ≤ 3% |

**Table S2. Image acquisition and processing data**

| Imaging module | Scanning metrics | | Reconstruction metrics | |
|---|---|---|---|---|
| **CT** | Voltage | 50 kV | Displaying Matrix | 512 x 512 |
| | Current | 0.5 mA | Slices | 500 |
| | Total frames | 360 | Filter | Soft |
| | Single frame acquisition time | 2000 ms | Pixel size | 0.136722 mm |
| | Step angle | 1.00° | Slice thickness | 0.18000 mm |
| **SPECT** | Scout image | Adopt CT scout image | Algorithm | OSEM |
| | Acquisition time | 25 min | Displaying Matrix | 60 x 60 |
| | | | Slices | 114 |
| | | | Iteration ordinal number | 40 |
| | | | Pixel size | 0.70000 mm |
| | | | Slice thickness | 0.70000 mm |

**Table S3. Fluorescence intensity-based quantitative analysis of DOTA-DZ-HX**

| | Unites | Time (h) | | | |
|---|---|---|---|---|---|
| | | **4** | **24** | **48** | **96** |
| **Tumor** | P/s/cm$^2$/sr (e+009) | 1.75 ± 0.10 | 1.83 ± 0.23 | 1.04 ± 0.13 | 0.49 ± 0.06 |
| **Tumor/ background** | ratio | 98.95 ± 2.89 | 108.15 ± 10.75 | 80.12 ± 10.97 | 65.22 ± 8.01 |

**Table S4. Organ biodistribution of [$^{177}$Lu]Lu-DOTA-DZ-HX in H1975 xenograft models***

| Organ | [$^{177}$Lu]Lu-DOTA-DZ-HX | | | | | |
|---|---|---|---|---|---|---|
| | 1 h | 4 h | 24 h | 48 h | 72 h | 96 h |
| **Blood** | 36.715 ± 7.213 | 24.936 ± 4.618 | 18.364 ± 6.168 | 7.831 ± 0.948 | 4.604 ± 0.732 | 0.685 ± 0.218 |
| **Heart** | 8.199 ± 1.354 | 6.430 ± 1.460 | 5.489 ± 0.668 | 3.705 ± 0.725 | 3.319 ± 0.501 | 0.935 ± 0.594 |
| **Liver** | 7.302 ± 2.060 | 5.788 ± 0.722 | 8.296 ± 0.452 | 8.127 ± 1.101 | 6.706 ± 0.724 | 2.335 ± 0.851 |
| **Spleen** | 5.111 ± 1.441 | 3.873 ± 0.684 | 5.726 ± 0.177 | 5.445 ± 0.916 | 5.313 ± 0.941 | 1.633 ± 0.906 |
| **Lung** | 9.895 ± 1.946 | 7.476 ± 0.863 | 5.391 ± 1.041 | 4.789 ± 0.759 | 3.835 ± 0.709 | 1.319 ± 0.557 |
| **Kidney** | 11.562 ± 2.412 | 14.228 ± 1.634 | 21.237 ± 2.254 | 22.129 ± 3.540 | 18.728 ± 3.240 | 7.099 ± 1.300 |
| **Stomach** | 3.550 ± 0.970 | 2.986 ± 0.501 | 2.867 ± 0.275 | 1.728 ± 0.184 | 1.446 ± 0.279 | 0.454 ± 0.279 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Intestine** | 4.130 ± 1.605 | 3.854 ± 0.614 | 2.503 ± 0.436 | 1.984 ± 0.426 | 1.762 ± 0.518 | 0.518 ± 0.374 |
| **Muscle** | 0.970 ± 0.338 | 1.580 ± 0.588 | 1.768 ± 0.592 | 1.500 ± 0.333 | 1.159 ± 0.171 | 0.234 ± 0.028 |
| **Bone** | 5.754 ± 2.292 | 2.259 ± 0.888 | 1.867 ± 0.297 | 1.509 ± 0.495 | 1.089 ± 0.192 | 0.492 ± 0.203 |
| **Brain** | 0.160 ± 0.023 | 0.762 ± 0.222 | 0.569 ± 0.363 | 0.275 ± 0.069 | 0.208 ± 0.046 | 0.054 ± 0.044 |
| **Tumor** | 5.754 ± 0.292 | 8.697 ± 0.866 | 13.501 ± 1.401 | 12.645 ± 1.192 | 12.055 ± 1.387 | 2.764 ± 0.518 |
| **T/B** | 0.160 ± 0.023 | 0.353 ± 0.029 | 0.779 ± 0.189 | 1.625 ± 0.164 | 2.632 ± 0.118 | 4.139 ± 0.572 |
| **T/L** | 0.826 ± 0.182 | 1.517 ± 0.201 | 1.629 ± 0.165 | 1.590 ± 0.343 | 1.798 ± 0.076 | 1.235 ± 0.244 |
| **T/K** | 0.512 ± 0.098 | 0.614 ± 0.056 | 0.638 ± 0.067 | 0.584 ± 0.121 | 0.649 ± 0.045 | 0.391 ± 0.055 |
| **T/M** | 3.128 ± 0.495 | 6.294 ± 2.848 | 8.135 ± 2.239 | 8.723 ± 2.003 | 10.482 ± 1.165 | 11.794 ± 1.460 |

*The data was in terms of %ID/g. The data are expressed as the mean ± SD (*n* = 4/group; for 96h *n* = 3), T/B: Tumor/Blood, T/L: Tumor/Liver, T/K: Tumor/Kidney, T/M: Tumor/Muscle.

**Table S5. Organ biodistribution of [$^{177}$Lu]Lu-DOTA-DZ-HX in HeLa xenograft models***

| Organ | [$^{177}$Lu]Lu-DOTA-DZ-HX | | | | |
|---|---|---|---|---|---|
| | 4 h | 24 h | 48 h | 72 h | 96 h |
| **Blood** | 37.471 ± 3.484 | 21.798 ± 2.698 | 10.056 ± 2.140 | 6.275 ± 0.600 | 4.692 ± 1.454 |
| **Heart** | 10.163 ± 1.454 | 7.989 ± 1.249 | 4.854 ± 0.665 | 4.195 ± 0.109 | 3.953 ± 0.524 |
| **Liver** | 8.931 ± 1.553 | 11.336 ± 1.021 | 9.242 ± 1.279 | 9.192 ± 0.356 | 8.193 ± 1.019 |
| **Spleen** | 6.251 ± 0.628 | 10.066 ± 1.166 | 6.935 ± 1.636 | 8.565 ± 2.325 | 6.998 ± 1.992 |
| **Lung** | 15.982 ± 1.754 | 12.323 ± 2.034 | 6.755 ± 0.289 | 6.712 ± 1.417 | 4.005 ± 0.609 |
| **Kidney** | 19.447 ± 1692 | 31.900 ± 1.088 | 25.780 ± 5.471 | 29.078 ± 2.768 | 25.091 ± 4.738 |

| | | | | | |
|---|---|---|---|---|---|
| **Stomach** | 4.975 ± 0.554 | 4.377 ± 0.226 | 2.416 ± 0.634 | 2.234 ± 0.083 | 2.476 ± 1.044 |
| **Intestine** | 5.912 ± 1.470 | 6.352 ± 3.061 | 2.719 ± 0.970 | 2.795 ± 0.714 | 2.846 ± 0.409 |
| **Muscle** | 2.800 ± 0.896 | 2.259 ± 0.406 | 1.533 ± 0.237 | 1.706 ± 0.202 | 1.525 ± 0.309 |
| **Bone** | 3.949 ± 0.751 | 2.875 ± 0.498 | 1.750 ± 0.456 | 2.157 ± 0.383 | 1.438 ± 0.301 |
| **Brain** | 0.804 ± 0.174 | 0.547 ± 0.049 | 0.313 ± 0.073 | 0.306 ± 0.182 | 0.208 ± 0.058 |
| **Tumor** | 11.892 ± 1.012 | 17.647 ± 4.098 | 16.522 ± 3.029 | 14.409 ± 2.743 | 11.938 ± 1.003 |
| **T/B** | 0.319 ± 0.032 | 0.804 ± 0.123 | 1.659 ± 0.220 | 2.297 ± 0.372 | 2.672 ± 0.549 |
| **T/L** | 1.350 ± 0.163 | 1.545 ± 0.271 | 1.798 ± 0.338 | 1.563 ± 0.247 | 1.463 ± 0.073 |
| **T/K** | 0.617 ± 0.096 | 0.551 ± 0.116 | 0.647 ± 0.097 | 0.494 ± 0.065 | 0.485 ± 0.063 |

| | | | | | |
|---|---|---|---|---|---|
| **T/M** | 4.600 ± 1.542 | 7.772 ± 1.061 | 11.079 ± 3.119 | 8.439 ± 1.081 | 8.012 ± 1.267 |

* The data was in terms of %ID/g. The data are expressed as the mean ± SD (*n* = 4/group), T/B: Tumor/Blood, T/L: Tumor/Liver, T/K: Tumor/Kidney, T/M: Tumor/Muscle.

**Table S6. The H1975 tumor volume of each group***

| H1975 Group | Tumor volume ($mm^3$) | | Tumor Growth Inhibition (%) at the end of the therapy |
|---|---|---|---|
| | at the beginning of the therapy | at the end of the therapy | |
| 37 MBq [$^{177}$Lu]Lu-DOTA-DZ-HX | 33.59 ± 8.76 | 10.01 ± 2.75 | 96.18 |
| 11.1 MBq [$^{177}$Lu]Lu-DOTA-DZ-HX | 30.77 ± 3.55 | 15.48 ± 7.51 | |
| 37 MBq [$^{177}$Lu]Lu-DOTA | 32.91 ± 7.23 | 196.16 ± 77.37 | |
| PBS | 35.81 ± 11.42 | 279.37 ± 115.53 | |

*The data are expressed as the mean ± SD ($n$ = 5/group).

**Table S7. The HeLa tumor volume and weight of each group***

| HeLa Group | Tumor volume ($mm^3$) | | Tumor weight | Tumor Growth Inhibition (%) at the end of the therapy |
|---|---|---|---|---|
| | at the beginning of the therapy | at the end of the therapy | | |
| 18.5 MBq [$^{177}$Lu]Lu-DOTA-DZ-HX | 80.86 ± 11.19 | 71.52 ± 28.86 | 0.04 ± 0.01 | 89.74 |
| 7.4 MBq [$^{177}$Lu]Lu-DOTA-DZ-HX | 73.66 ± 7.52 | 86.41 ± 23.76 | 0.06 ± 0.02 | |
| PBS | 86.97 ± 6.55 | 749.67 ± 154.30 | 0.64 ± 0.15 | |

*The data are expressed as the mean ± SD ($n$ = 5/group).

**Table S8. Quantitative Evaluation of Tumor Tissue Apoptosis and Immunohistochemical Profiling***

| Tumor | Apoptosis rate (%) | | | % DAB Positive Tissue | |
|---|---|---|---|---|---|
| | High | Low | PBS | HIF-1α | OATP2B1 |
| **H1975** | 60.92 ± 7.60 | 18.57 ± 7.37 | 2.02 ± 0.41 | 38.86 | 32.15 |
| **HeLa** | 27.30 ± 10.49 | 13.28 ± 0.03 | 0.00 ± 0.00 | 58.87 | 79.38 |

*The data are expressed as the mean ± SD ($n$ = 3/group).