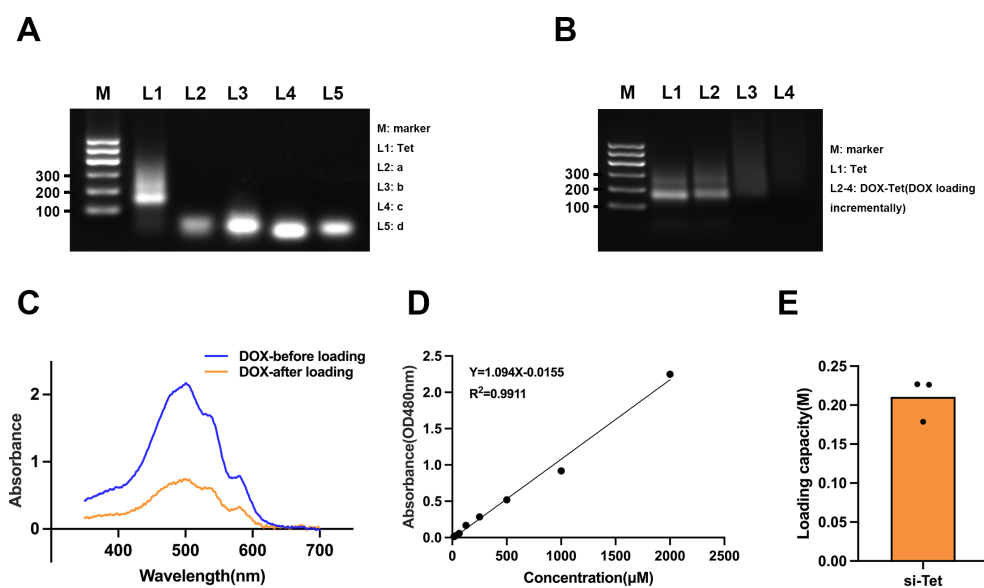
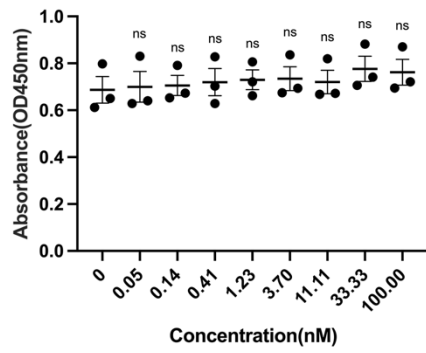
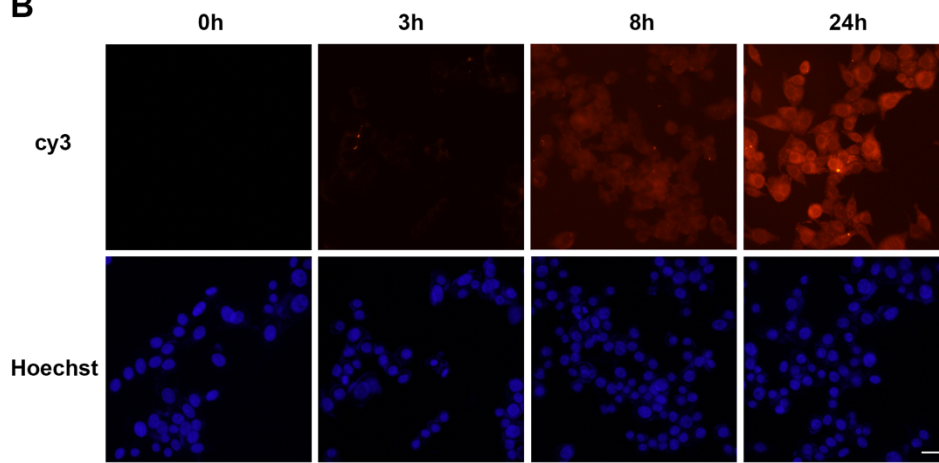


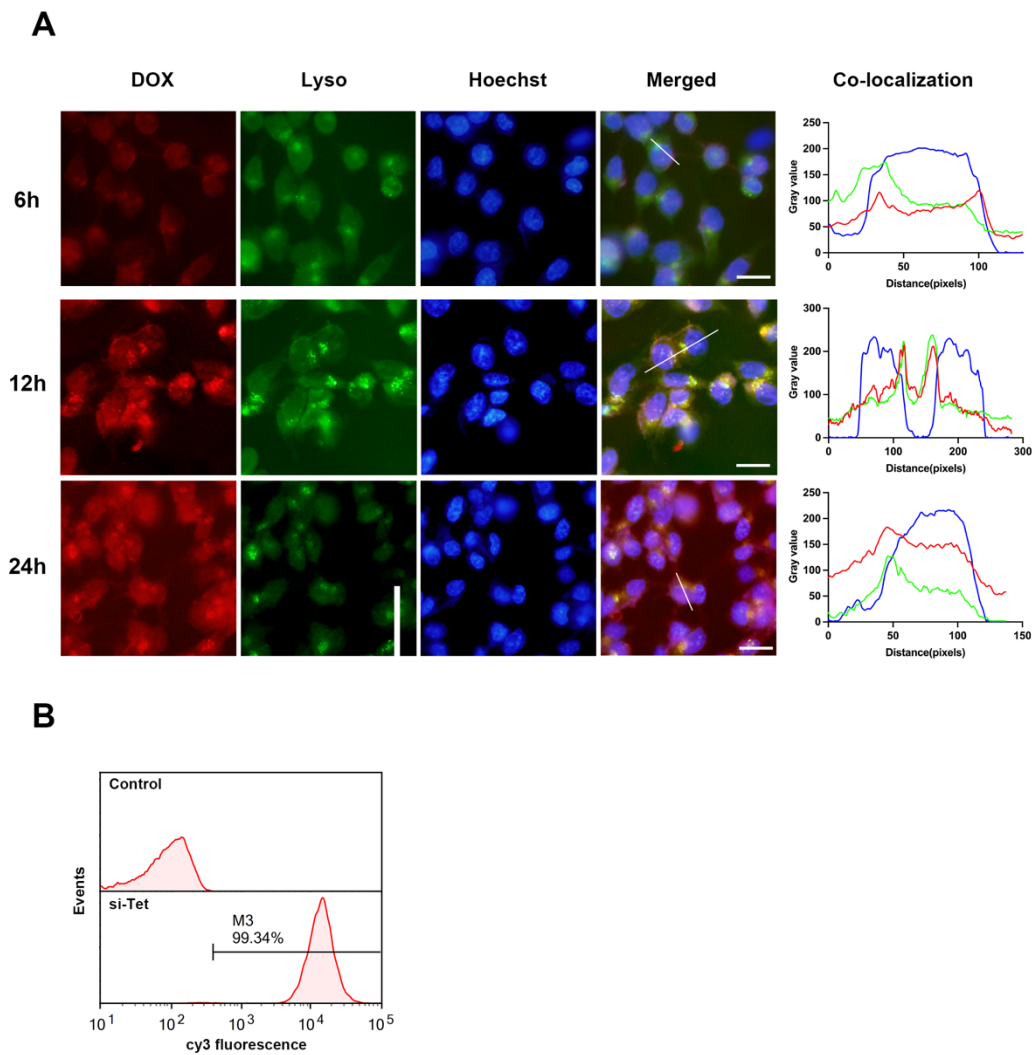
**Figure S1 RNF8 expression is increased in both colon and rectal cancer.** (A) and (B) RNF8 expression in colon and rectal cancer samples was analyzed based on lymph node metastasis status. N0: regional lymph node metastasis; N1: Metastases in 1 to 3 axillary lymph nodes; N2: Metastases in 4 to 9 axillary lymph nodes. (C) RNF8 transcript levels in rectal cancer samples from the TCGA database were analyzed using UALCAN. (D) Analysis of RNF8 expression levels in samples of rectal cancer cases at different stages from the TCGA database. (E) RNF8 was detected by immunohistochemical staining on tissue microarray containing 48 pairs of colon cancer samples and adjacent normal tissues. The singular column represents the colon cancer sample, while the double column indicates the corresponding adjacent normal tissue. The red boxes in the figure identify those that were not counted. \* represents  $p < 0.05$  and \*\*\*\* represents  $p < 0.0001$ .



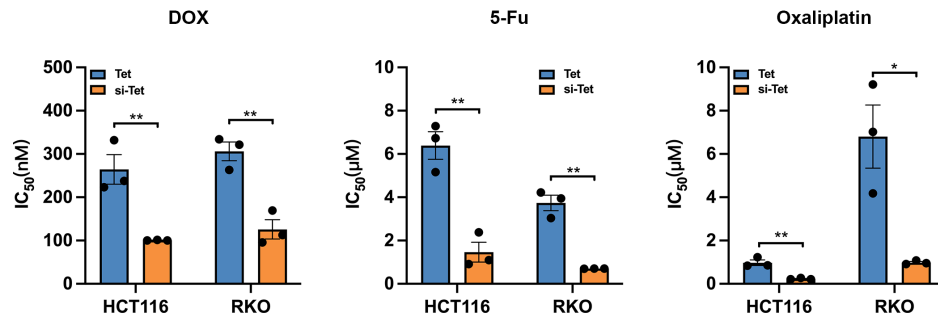
**Figure S2 Physical characterization of FNA and drug-loaded FNA.** (A) Gel electrophoresis analysis of Tet and four DNA single strands. And a, b, c, and d represent the four single strands used to assemble the DNA tetrahedron. (B) Gel electrophoresis analysis of Tet as well as DOX-Tet. (C) UV-vis absorption curves of DOX before and after loading. (D) Standard curve for quantification of DOX. (E) Bar graph indicates the drug loading capacity of si-Tet to DOX.

**A****B**

**Figure S3 The safety and cellular internalization of FNA were analyzed.** (A) HCT116 were incubated with different concentrations of Tet, and the cell viability was detected by CCK-8 assay. (B) Cells were incubated with cy3-si-Tet, and the intracellular fluorescence intensity was analyzed by fluorescence microscopy at the indicated time points. Scale bar = 50  $\mu$ m. ns = no significance.



**Figure S4 Cellular internalization of FNAs.** (A) HCT116 cells were treated with si-DOX-Tet for different times. The subcellular localization was analyzed by fluorescence microscope, and lysosome was labeled with Lyso-Tracker Green. Scale bar = 20  $\mu\text{m}$ . (B) Cells were incubated with cy3-si-Tet for 24 h, and intracellular fluorescence intensity was analyzed by flow cytometry.



**Figure S5** Bar graphs show the median lethal dose of the three drugs to the HCT116 and RKO cells. \* represents  $p < 0.05$  and \*\* represents  $p < 0.01$ .

**Table S1: Primers designed for detection of indicated gene expression**

**in qPCR**

| <b>Gene</b>  | <b>Forward primer (5'→3')</b>  | <b>Reverse primer (5'→3')</b>  |
|--------------|--------------------------------|--------------------------------|
| <b>RNF8</b>  | <b>GGAGAAAAGGACCTGAAGCAACA</b> | <b>GCTTCAAAGTCCTTCTTGCTGCG</b> |
| <b>ABCB1</b> | <b>GCTGTCAAGGAAGCCAATGCCT</b>  | <b>TGCAATGGCGATCCTCTGCTTC</b>  |
| <b>ABCC1</b> | <b>CCGTGTACTCCAACGCTGACAT</b>  | <b>ATGCTGTGCGTGACCAAGATCC</b>  |
| <b>ABCG2</b> | <b>GTTCTCAGCAGCTCTTCGGCTT</b>  | <b>TCCTCCAGACACACCACGGATA</b>  |
| <b>GAPDH</b> | <b>GTCTCCTCTGACTTCAACAGCG</b>  | <b>ACCACCCTGTTGCTGTAGCCAA</b>  |

**Table S2: The sequences of the tetrahedral FNAs**

| <b>Strand</b>                         | <b>Base sequence (5'→3')</b>   |
|---------------------------------------|--|
| <b>a</b>                              | ACATTCCTAAGTCTGAAACATTACAGCTTGCTACA<br>CGAGAAGAGCCGCCATAGTA                  |
| <b>b</b>                              | ATATCACCAGGCAGTTGACAGTGTAGCAAGCTGTA<br>ATAGATGCGAGGGTCCAATAC                 |
| <b>cy3-b</b>                          | cy3-ATATCACCAGGCAGTTGACAGTGTAGCAAGCTGTA<br>ATAGATGCGAGGGTCCAATAC             |
| <b>c</b>                              | ATCAACTGCCTGGTGATAAAACGACACTACGTGGGA<br>ATCTACTATGGCGGCTCTTC                 |
| <b>d</b>                              | ATTCAGACTTAGGAATGTGCTTCCCACGTAGTGTGCG<br>TTTGTATTGGACCCTCGCAT                |
| <b>d with<br/>sticky end</b>          | ATTCAGACTTAGGAATGTGCTTCCCACGTAGTGTGCGTT<br>TGTATTGGACCCTCGCATT TTTGGTTTTTGGG |
| <b>siRNF8<br/>with<br/>sticky end</b> | sense: UGCGGAGUAUGAAUAUGAATT<br>antisense: UUCAUAUUCUAUCUCCGCATTCCCAAAAACC   |

**Table S3: Expression of RNF8 in Colon adenocarcinoma (COAD)**

| <b>Category</b>                 | <b>TCGA samples</b>     | <b>low</b> | <b>q1</b> | <b>median</b> | <b>q3</b> | <b>high</b> |
|---------------------------------|-------------------------|------------|-----------|---------------|-----------|-------------|
| <b>sample types</b>             | <b>Normal (n = 41)</b>  | 2.565      | 3.526     | 3.824         | 4.187     | 4.736       |
|                                 | <b>Tumor (n = 286)</b>  | 3.221      | 5.47      | 6.344         | 7.536     | 10.476      |
| <b>individual cancer stages</b> | <b>Normal (n = 41)</b>  | 2.565      | 3.526     | 3.824         | 4.187     | 4.736       |
|                                 | <b>Stage1 (n = 45)</b>  | 3.221      | 5.044     | 6.403         | 7.105     | 10.006      |
|                                 | <b>Stage2 (n = 110)</b> | 3.252      | 5.403     | 6.238         | 7.486     | 10.172      |
|                                 | <b>Stage3 (n = 80)</b>  | 4.071      | 5.495     | 6.341         | 7.926     | 11.828      |
|                                 | <b>Stage4 (n = 39)</b>  | 4.063      | 5.661     | 6.393         | 7.122     | 9.834       |
| <b>nodal metastasis status</b>  | <b>Normal (n = 41)</b>  | 2.565      | 3.526     | 3.824         | 4.187     | 4.736       |
|                                 | <b>N0 (n = 166)</b>     | 3.221      | 5.452     | 6.344         | 7.53      | 10.172      |
|                                 | <b>N1 (n = 70)</b>      | 4.288      | 5.398     | 6.133         | 7.164     | 9.762       |
|                                 | <b>N2 (n = 47)</b>      | 4.063      | 5.79      | 6.395         | 7.8       | 10.476      |

**q: quarter; N0: regional lymph node metastasis; N1: Metastases in 1 to 3 axillary**

**lymph nodes; N2: Metastases in 4 to 9 axillary lymph nodes**



**Table S4: Expression of RNF8 in Rectum adenocarcinoma (READ)**

| Category                 | TCGA samples       | low   | q1    | median | q3    | high   |
|--------------------------|--------------------|-------|-------|--------|-------|--------|
| sample types             | Normal<br>(n = 10) | 3.595 | 3.89  | 4.098  | 4.79  | 5.557  |
|                          | Tumor<br>(n = 166) | 1.479 | 4.559 | 5.854  | 7.237 | 11.025 |
| individual cancer stages | Normal<br>(n = 10) | 3.595 | 3.89  | 4.098  | 4.79  | 5.557  |
|                          | Stage1<br>(n = 30) | 1.804 | 4.273 | 5.575  | 6.689 | 9.147  |
|                          | Stage2<br>(n = 51) | 1.839 | 4.408 | 5.722  | 6.787 | 9.479  |
|                          | Stage3<br>(n = 51) | 1.479 | 4.822 | 5.764  | 6.869 | 10.921 |
|                          | Stage4<br>(n = 24) | 2.852 | 4.664 | 6.131  | 7.501 | 10.631 |
| nodal metastasis status  | Normal<br>(n = 10) | 3.595 | 3.89  | 4.098  | 4.79  | 5.557  |
|                          | N0<br>(n = 84)     | 1.804 | 4.366 | 5.644  | 6.768 | 9.479  |
|                          | N1<br>(n = 45)     | 1.479 | 4.865 | 6.23   | 8.259 | 11.606 |
|                          | N2<br>(n = 33)     | 2.221 | 4.598 | 5.75   | 7.089 | 9.305  |

**q: quarter; N0: regional lymph node metastasis; N1: Metastases in 1 to 3 axillary**

**lymph nodes; N2: Metastases in 4 to 9 axillary lymph nodes**