Electronic Supplementary Information

Dynamics of delivering aptamer targeted nano-drug into cell

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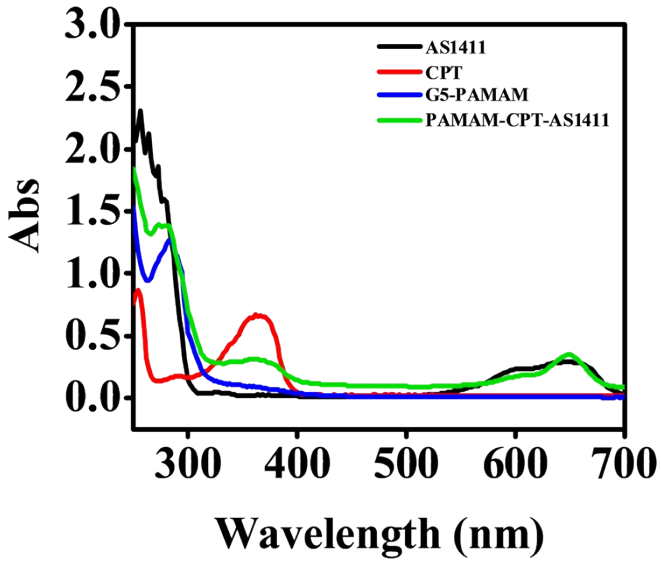

Fig. S1 UV-Vis Spectra of aptamer AS1411 (black), CPT (red), G5-PAMAM (blue), and PAMAM-CPT-AS1411 (green).

The prepared PAMAM-CPT-AS1411 nano-drugs were characterized by UV-Vis spectroscopy, and the results are shown in Fig. S1. The characteristic peak of AS1411-Cy5 is 650 nm (black),[1] the characteristic peak of CPT is 365 nm (red),[2] and the characteristic peak of G5-PAMAM is 278 nm (blue).[3] The UV-Vis spectrum of PAMAM-CPT-AS1411 nano-drug (green) contains the characteristic peaks of AS1411-Cy5, CPT, and G5-PAMAM. The results showed that PAMAM-CPT-AS1411 nano-drugs have been successfully synthesized.

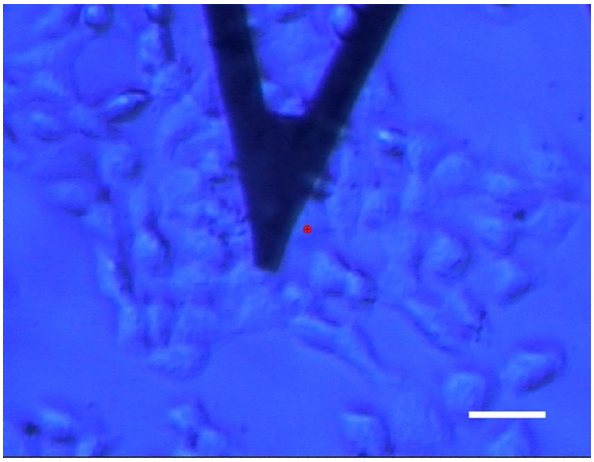

Fig. S2 The optical image of the AFM tip cantilever locating above the living A549 cell. (Scale bar: 60 μm).

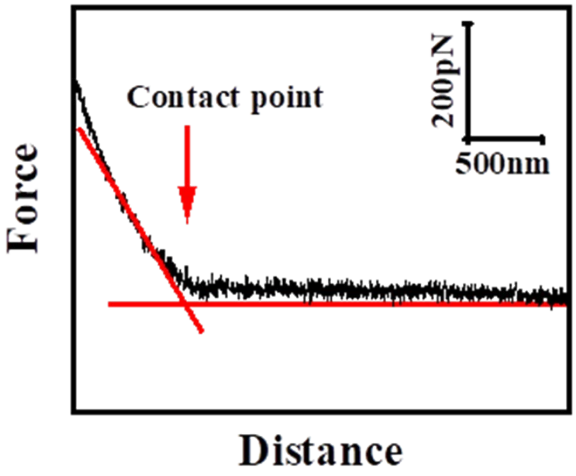

Fig. S3 The contact point between the PAMAM-CPT-AS1411 modified AFM tip and the cell surface. The contact point is the intersection of the slope (red line) and the flat part in the force-distance curve, indicating by the red arrow.

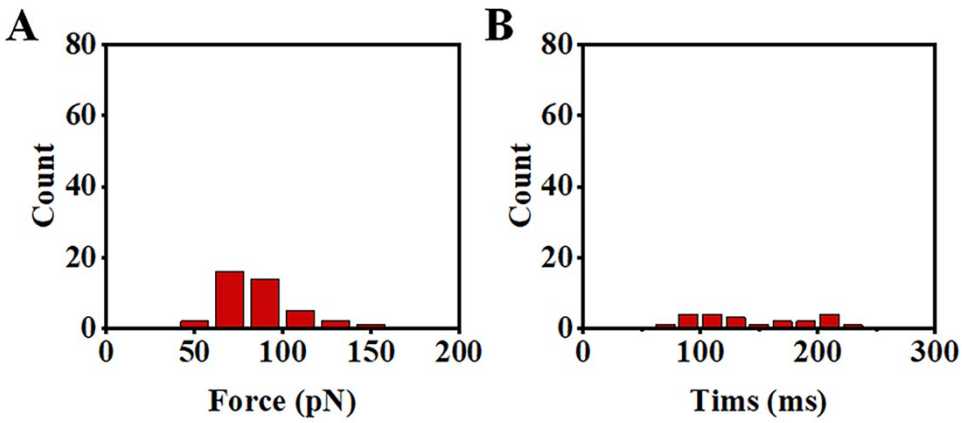

Fig. S4 Force and duration distribution after blocking with free AS1411. (A) Force distribution of PAMAM-CPT-AS1411 endocytic uptake after inhibiting with free AS1411. (B) Duration distribution of PAMAM-CPT-AS1411 endocytic uptake after inhibiting with free AS1411. The results were calculated by randomly selecting approximately 1000 force tracing curves.

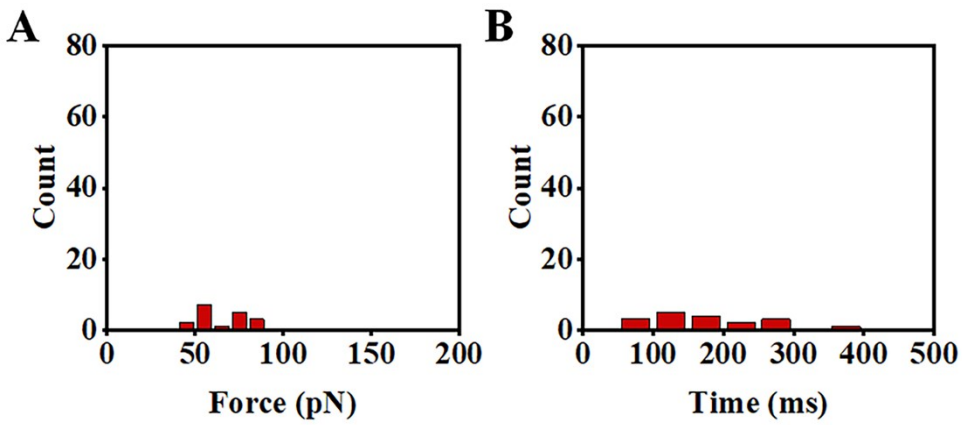

Fig. S5 Force and duration distribution after blocking with endostatin. (A) Force distribution of PAMAM-CPT-AS1411 endocytic uptake after blocking with endostatin. (B) Duration distribution of PAMAM-CPT-AS1411 endocytic uptake after blocking with endostatin. The results were calculated by randomly selecting approximately 1000 force tracing curves.

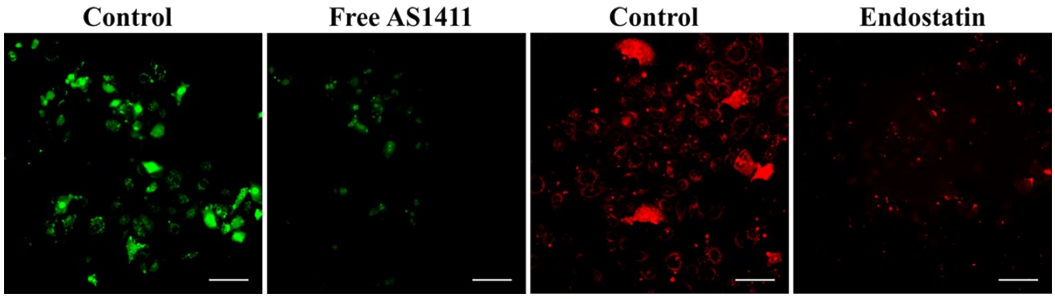

Fig. S6 Fluorescence images of A549 cells uptake PAMAM-CPT-AS1411 before and after blocking with free AS1411 and Endostatin. (Scale bar: 100 μm).

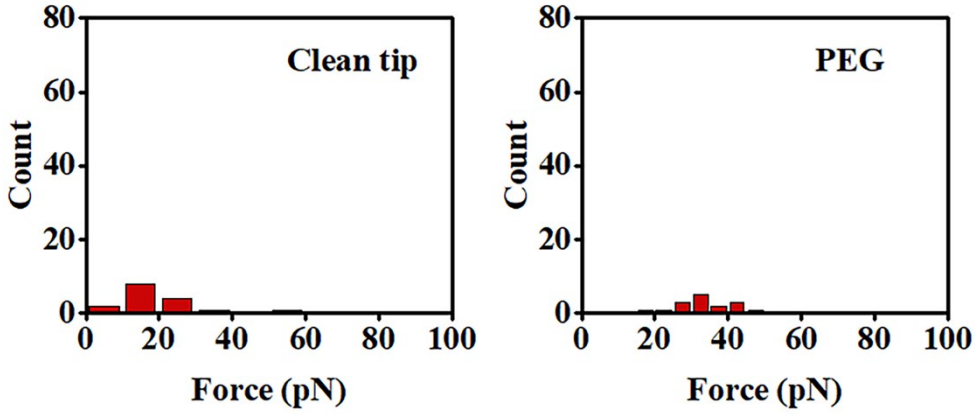

Fig. S7 Force distribution measured by force tracing on A549 cells with unmodified AFM tip (clean tip) and PEG-modified AFM tip (PEG). The results were calculated by randomly selecting approximately 1000 force tracing curves.

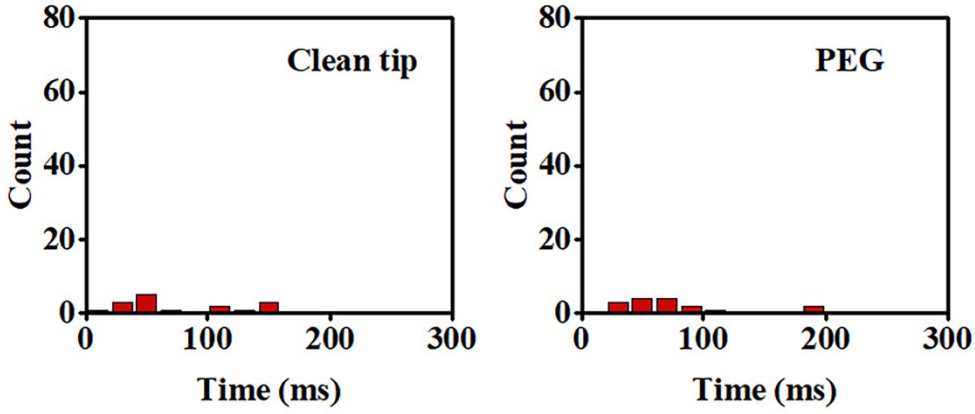

Fig. S8 Duration distribution measured by force tracing on A549 cells with unmodified AFM tip (clean tip) and PEG-modified AFM tip (PEG). The results were calculated by randomly selecting approximately 1000 force tracing curves.

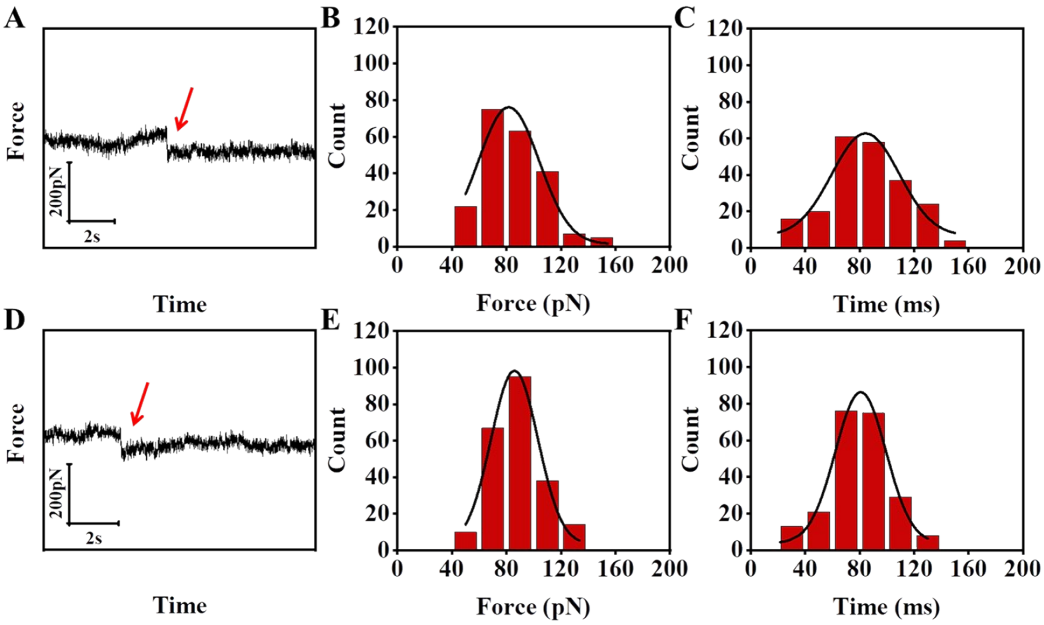

Fig. S9 The dynamic parameters of a single nano-drug entry cancer and normal cells. (A) Typical force tracing curve for PAMAM-CPT entry into A549 cell. (B, C) Force and duration distribution of PAMAM-CPT entry into the A549 cells, respectively. (n≈200). (D) Typical force tracing curve of PAMAM-CPT-AS1411 entry into Vero cells. (E, F) Force and duration distribution of PAMAM-CPT-AS1411 entry into the Vero cells, respectively. (n≈200).

A typical force tracing curve of PAMAM-CPT entry A549 cell is shown in Fig. S9A. The force distributes from 50.99 to 140.42 pN with a mean value of 85.04 ± 19.09 pN (Fig. S9B), and the duration varies from 20.15 to 153.6 ms with a mean value of 85.16 ± 28.39 ms (Fig. S9C). A typical force tracing curve of PAMAM-CPT-AS1411 entry Vero cell is shown in Fig. S9D. The corresponding force distributes from 53.23 to

130.44 pN with a mean value of 88.60 ± 17.92 pN (Fig. S9E), and the duration varies from 35.5 to 129.2 ms with a mean value of 81.20 ± 18.98 ms (Fig. S9F).

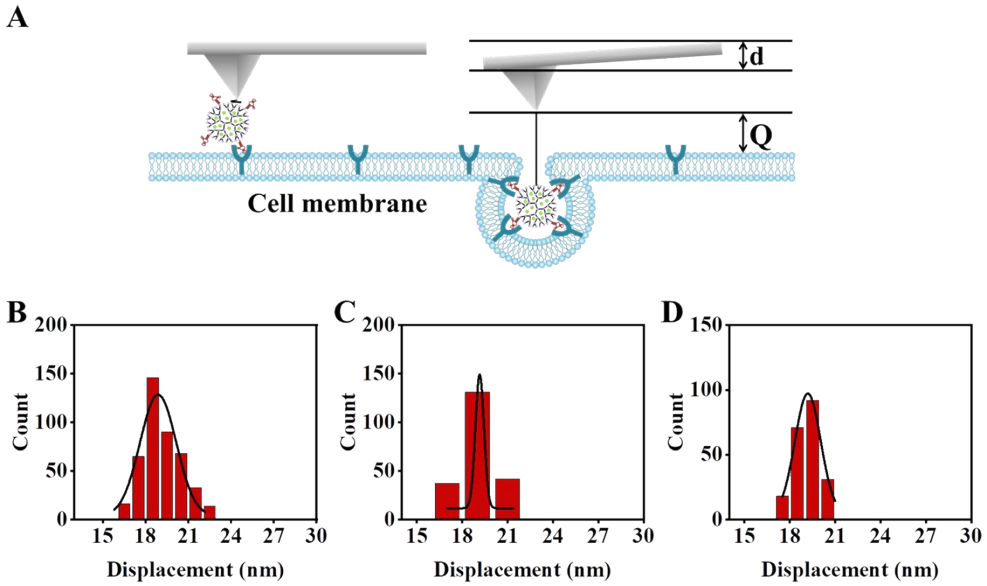

Fig. S10 The displacement of nano-drug entry cell. (A) The displacement diagram of nano-drug during the entry cell process. (B) Displacement distribution of PAMAM-CPT-AS1411 entry A549 cell. The displacement distribution is in the range of 15.80-22.14 nm with an average value of 18.82 ± 1.89 nm. (n≈450). (C) Displacement distribution of PAMAM-CPT entry A549 cell. The displacement distribution is in the range of 16.63-21.38 nm with a mean value of 18.77 ± 2.16 nm. (n≈200). (D) Displacement distribution of PAMAM-CPT-AS1411 entry Vero cell. The displacement distribution is in the range of 16.80-20.95 nm with a mean value of 18.96 ± 1.19 nm. (n≈200).

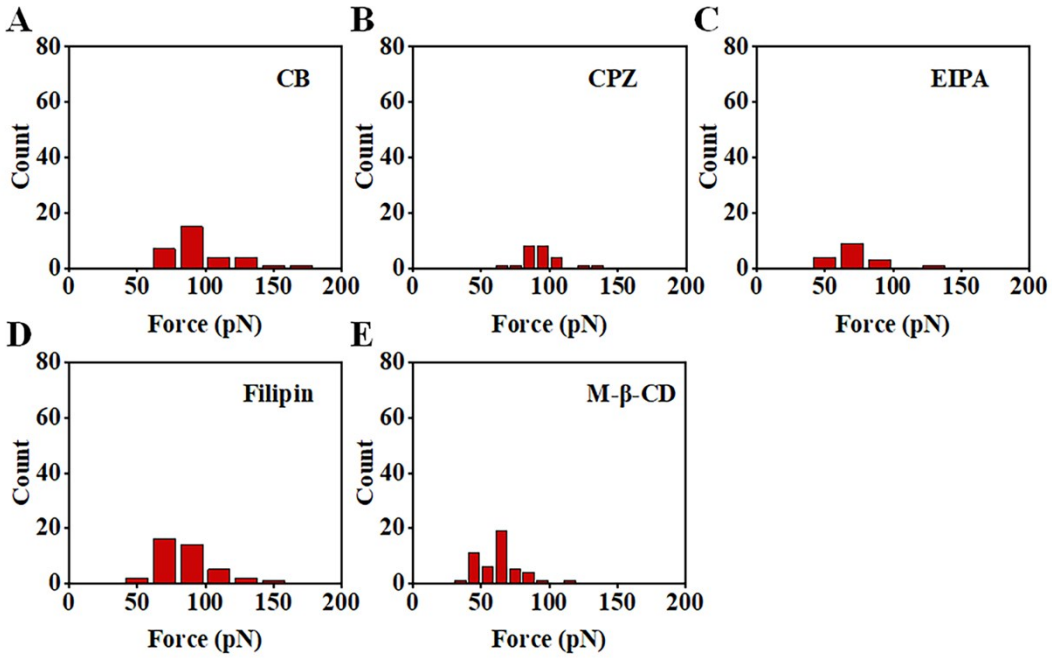

Fig. S11 Force distribution after blocking. Force distribution of PAMAM-CPT-AS1411 endocytic uptake after blocking with (A) CB, (B) CPZ, (C) EIPA, (D) Filipin, and (E) M-β-CD. The results were calculated by randomly selecting approximately 1000 force tracing curves.

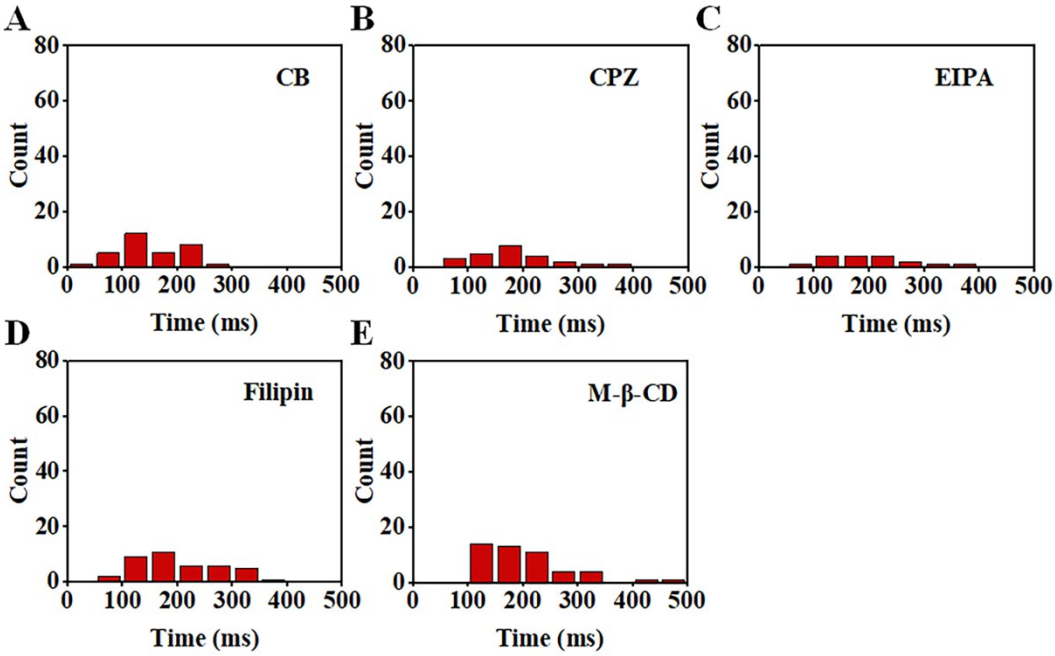

Fig. S12 Duration distribution after blocking. Duration distribution of PAMAM-CPT-AS1411 endocytic uptake after blocking with (A) CB, (B) CPZ, (C) EIPA, (D) Filipin, and (E) M-β-CD. The results were calculated by randomly selecting approximately 1000 force tracing curves.

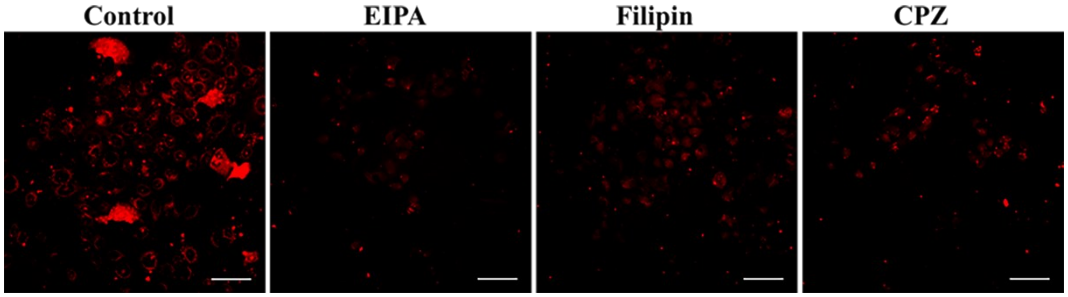

Fig. S13 Fluorescence images of A549 cells uptake PAMAM-CPT-AS1411 before (Control) and after blocking with inhibitors (EIPA, Filipin, and CPZ). (Scale bar: 100 μm).

References

1. S. Yoneoka, Y. Nakagawa, K. Uto, K. Sakura, T. Tsukahara and M. Ebara, *Sci. Technol. Adv. Mater.*, 2019, **20**, 291-304.
2. D. Dvoranová, M. Bobenicová, S. Soralová and M. Breza, *Chem. Phys. Lett.*, 2013, **580**, 141-144.
3. X. Bi, X. Shi and J. R. Baker, *J. Biomater. Sci., Polym. Ed.*, 2008, **19**, 131-142.