Electronic Supplementary Material (ESI) for Nanoscale.
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SUPPLEMENTARY FIGURES

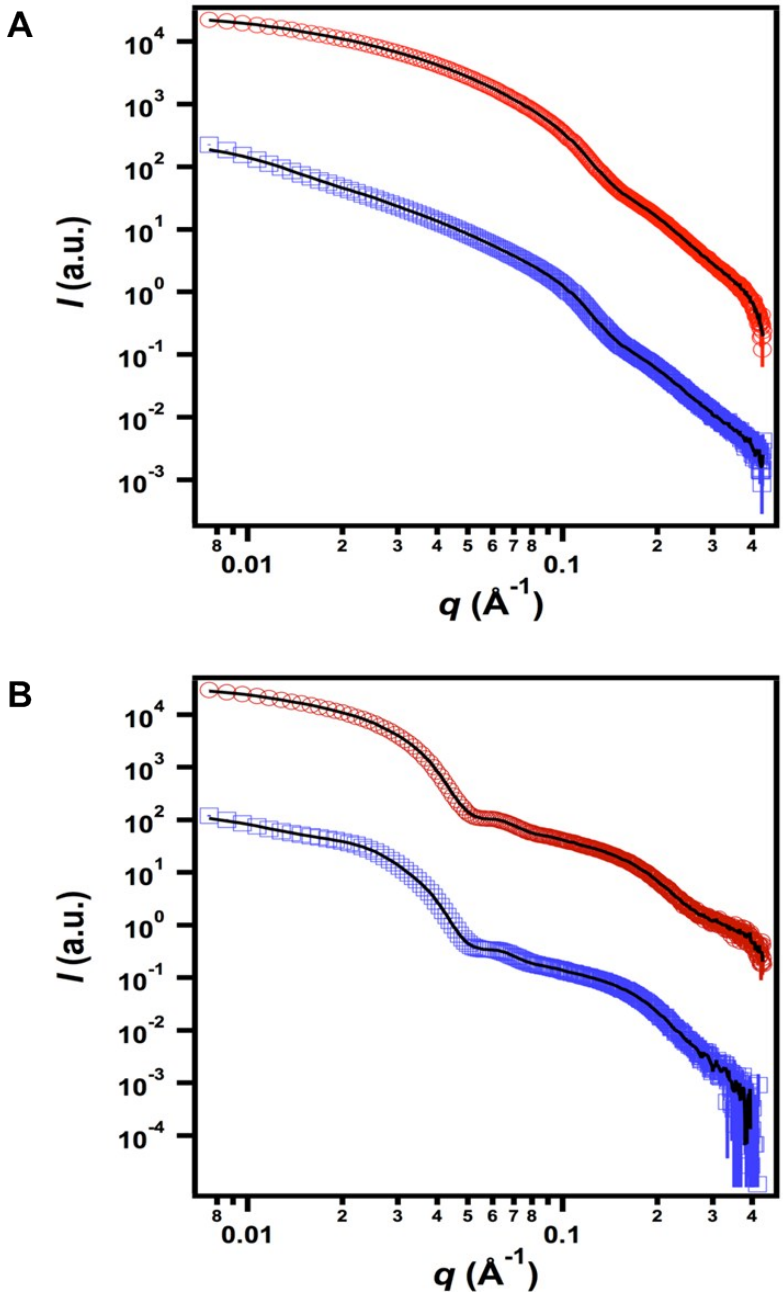

Fig. S1. (A) Small angle X-ray scattering curves for Pt5 before (red) and after cell medium exposure (blue) with fits performed using form factor for spherical particles adding a Schulz sphere size distribution with Sticky Hard Sphere Structure factor (black solid lines). **(B)** Small angle X-ray scattering curves for Pt20 before (red) and after cell medium exposure (blue) with fits performed using form factor for spherical particles adding a Schulz sphere size distribution with Sticky Hard Sphere Structure factor (black solid lines).

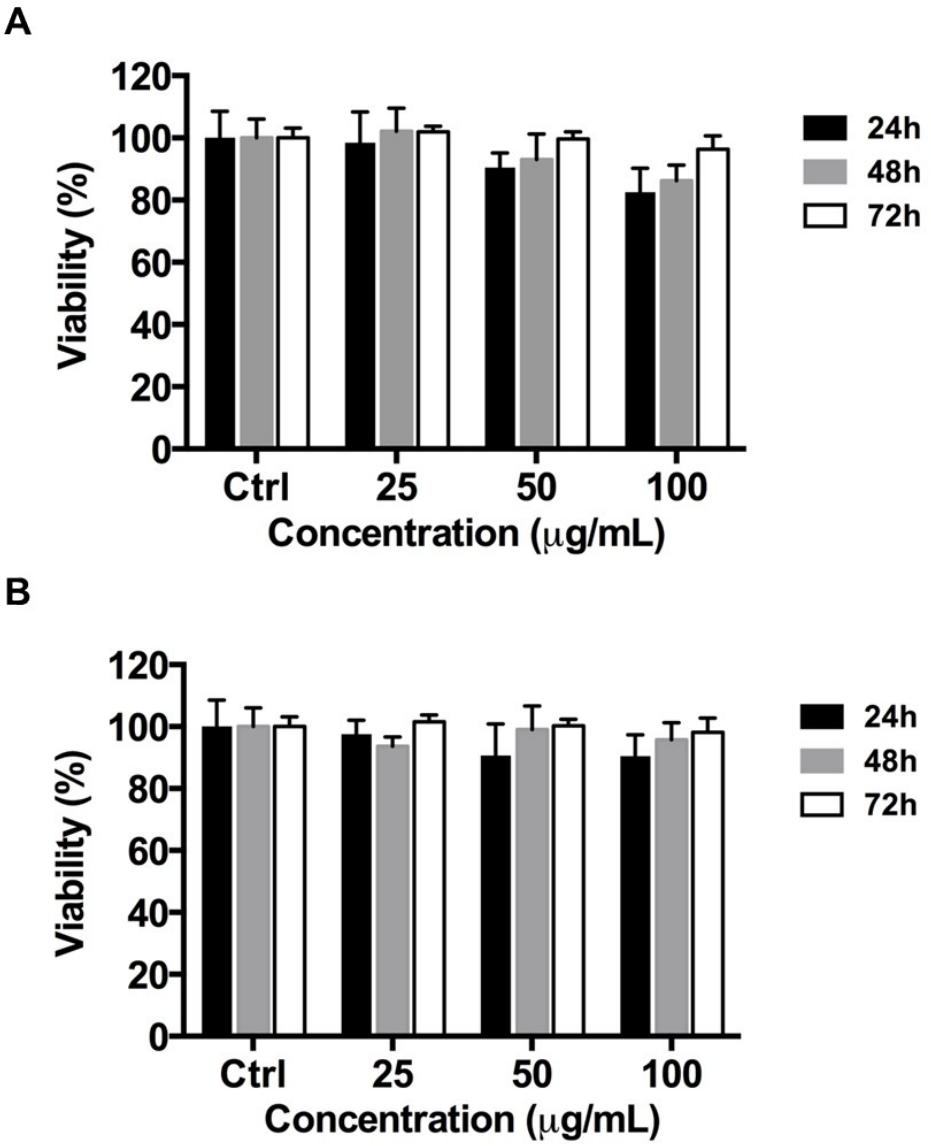

Fig. S2. Viability of MCF7 cells exposed for 24, 48, and 72 hours to increasing doses of Pt5 **(A)** and Pt20 **(B)**. Viability of NPs-treated cells is expressed as relative to untreated control cells (Ctrl). Data are reported as mean ± SD. The experiment was independently performed at least three times.

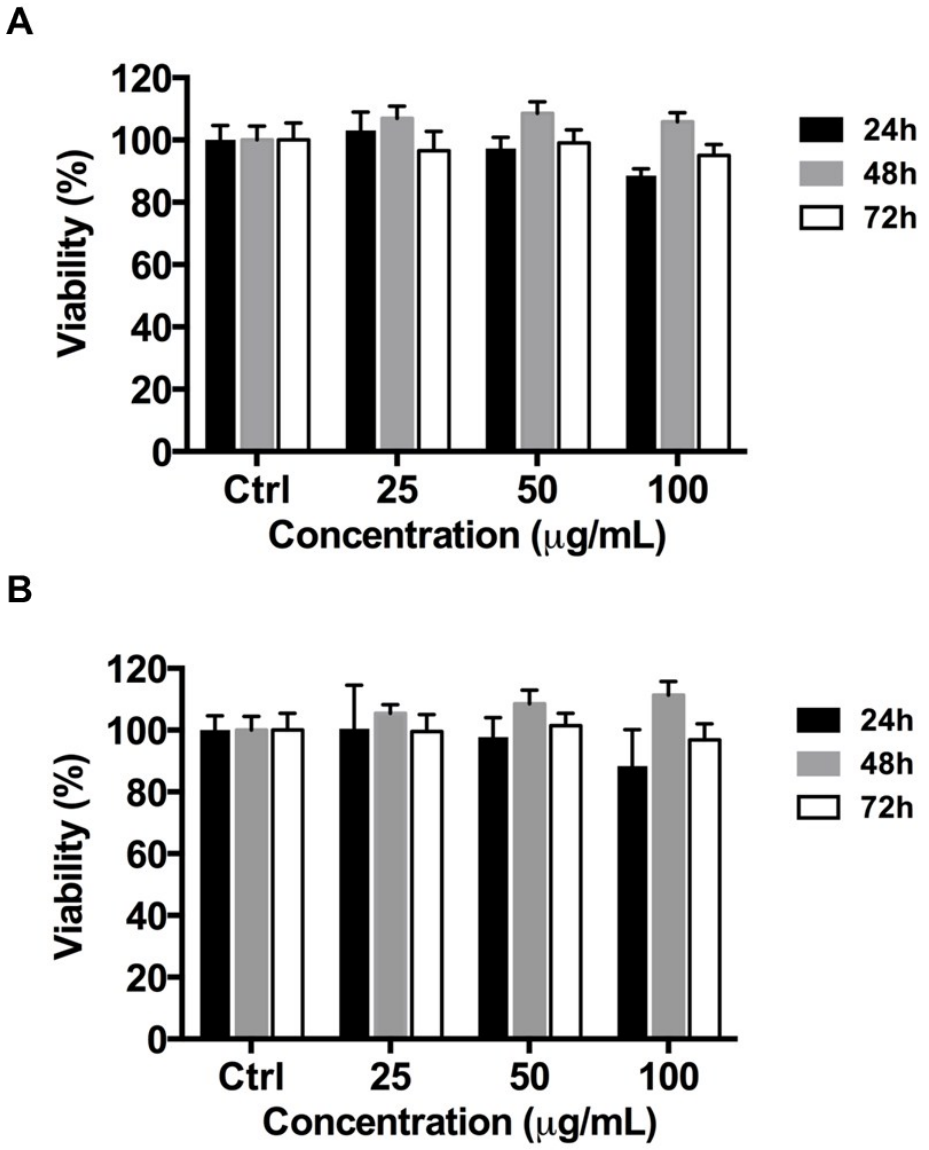

Fig. S3. Viability of Caco-2 cells exposed for 24, 48, and 72 hours to increasing doses of Pt5 **(A)** and Pt20 **(B)**. Viability of NPs-treated cells is expressed as relative to untreated control cells (Ctrl). Data are reported as mean ± SD. The experiment was independently performed at least three times.

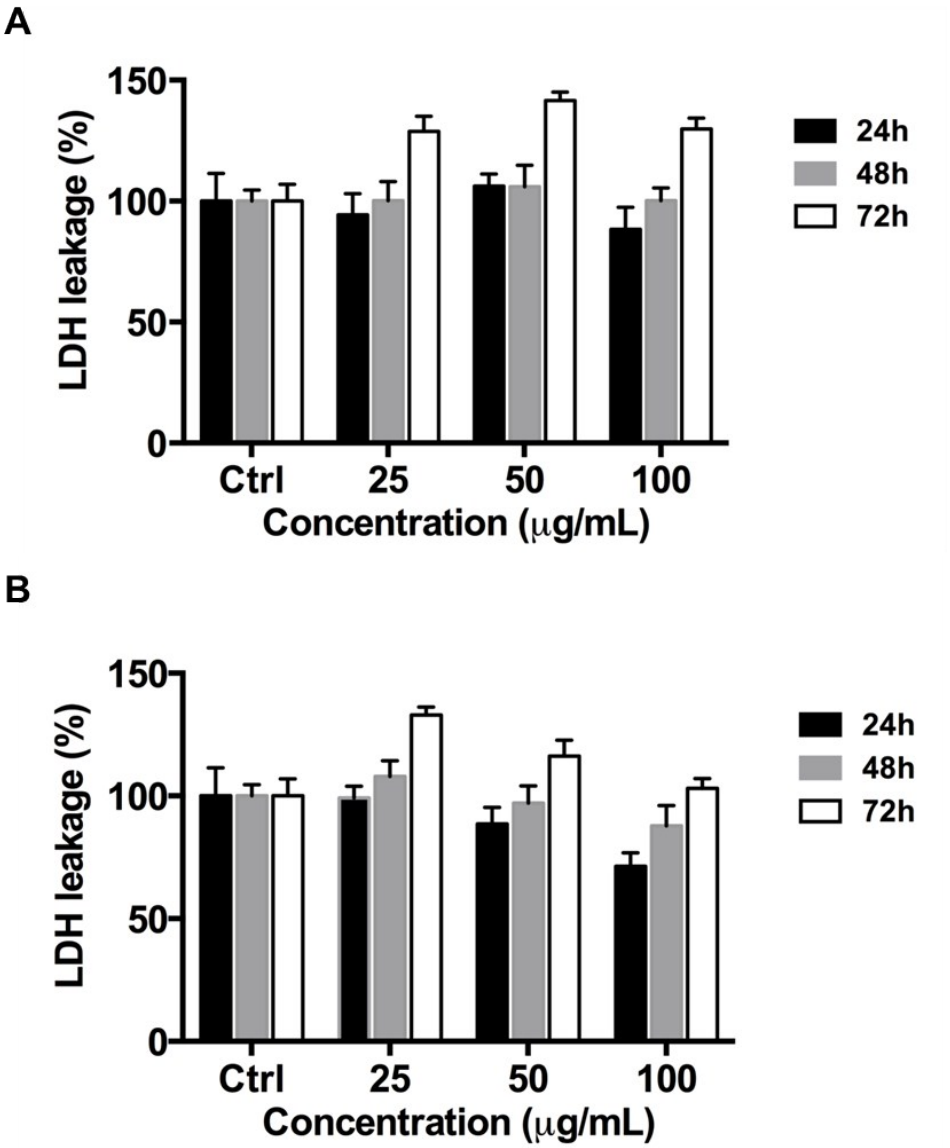

Fig. S4. LDH release in HeLa cells exposed for 24, 48, and 72 hours to increasing doses of Pt5 **(A)** and Pt20 **(B)**. Percentage of LDH leakage of NPs-treated cells is expressed relative to untreated control cells (Ctrl). Data are reported as mean ± SD. The experiment was independently performed at least three times. Data show higher values of LDH leakage percentage at higher incubation time (72h) for both Pt5 and Pt20 nanoparticles compared to non-treated control cells. These increases are non-statistically significant and they are not dose-dependent.

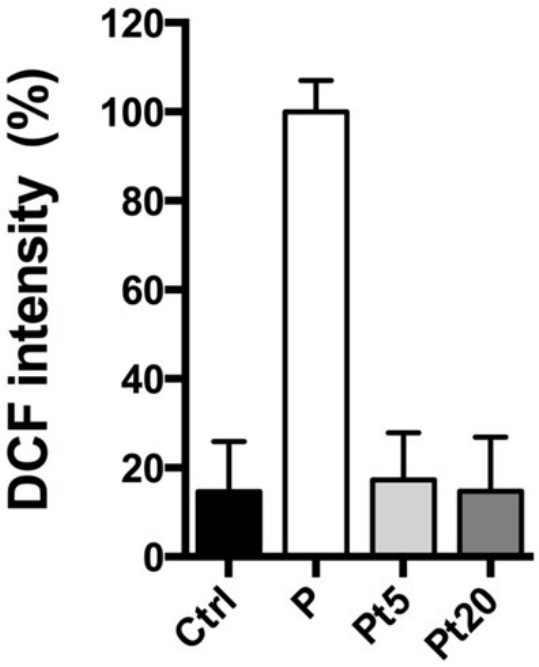

Fig. S5. ROS levels in HeLa cells exposed to Pt5 and Pt20 (50 μg/mL) for 24 hours evaluated by DCF assay. ROS generation of NPs-treated cells is expressed relative to untreated control cells (Ctrl). As a positive control (P), cells were incubated with 100 μM H_2O_2. Data are reported as mean ± SD from three independent experiments.

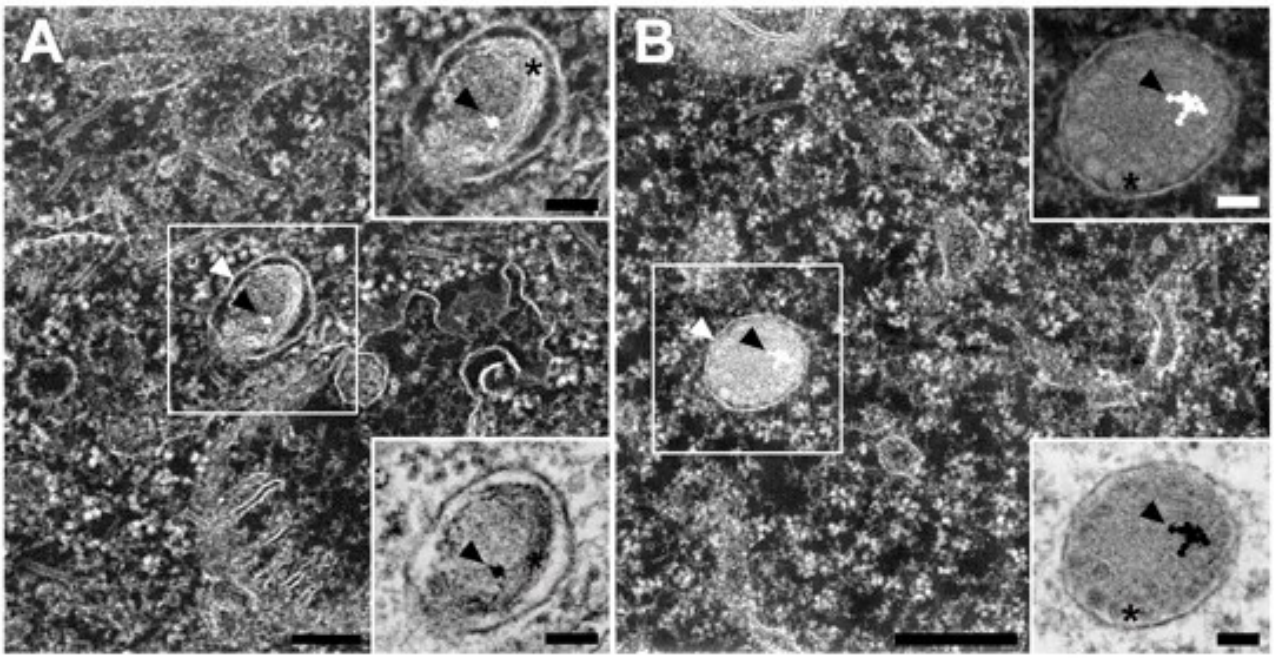

Fig. S6. Representative low magnification HAADF STEM micrographs through the ribosome rich cytoplasm of HeLa cells loaded respectively with 5 nm **(A)** and 20 nm **(B)** Pt NPs. Note in both micrographs a late endosome/lysosome (white arrowheads) containing the 5 nm **(A)** and 20 nm **(B)** Pt NPs respectively (black arrowheads). The Insets show higher magnification through the regions boxed in A and B, in dark (up) and digitally inverted bright field (bottom). Note the presence of Pt Nps (black arrowheads) close to a multi-membrane stack (in A Inset, asterisk) and to several vesicles (in B Inset, asterisk). Scale bars are 200 nm in A, 500 nm in B and 100 nm in A and B Insets.

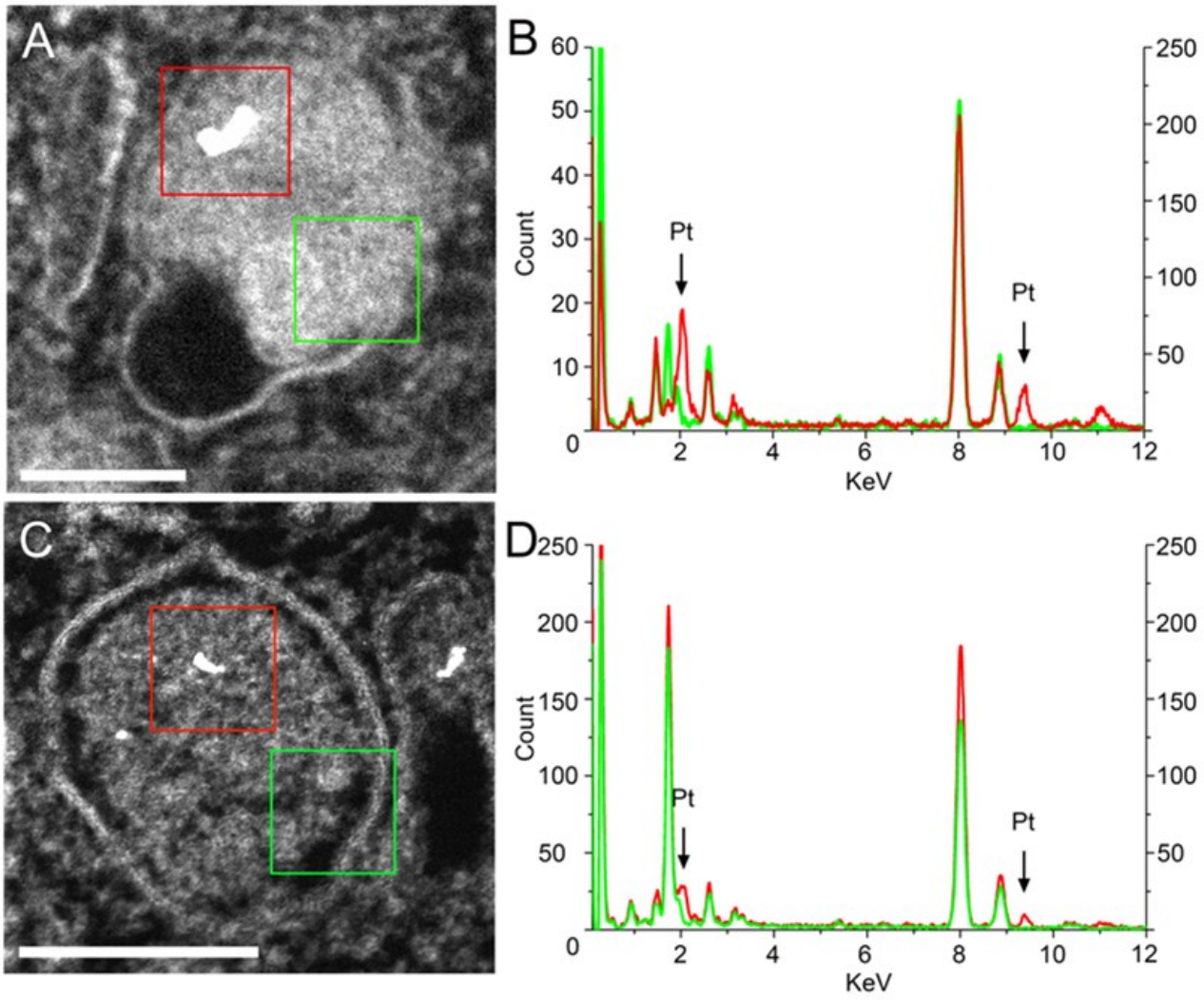

Fig. S7. Energy dispersive X-ray spectroscopy (EDXS) analysis on sections of HeLa cells loaded with Pt20 (**A** and **B**) and Pt5 (**C** and **D**). **(A)** High angular annular dark field (HAADF) STEM image of a late endosome containing numerous Pt20 (red box). **(B)** Compositional Pt mapping of the red and green regions boxed in (**A**). Pt is present exclusively in the region containing NPs. **(C)** HAADF STEM image of a late endosome containing numerous Pt5 (red box). **(D)** Compositional Pt mapping of the red and green regions boxed in C. Pt is present exclusively in the region containing NPs. Scale bars are 200 nm.

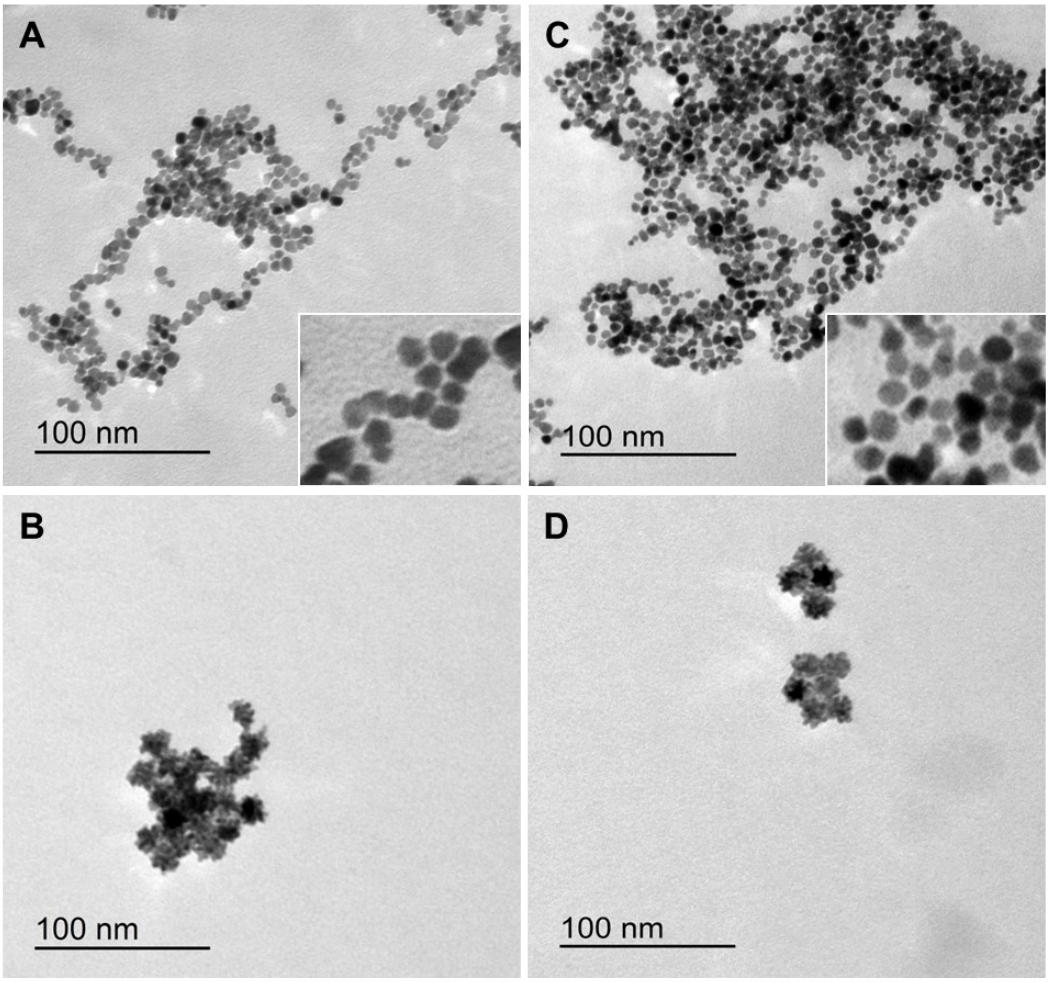

Fig. S8. TEM images comparison between NPs kept at neutral pH (**A**, Pt5; **B**, Pt20) and acidic pH (**C**, Pt5; **D**, Pt20). Insets in **A** and **B** are digital zoom of the images.

Table S1. Fitting parameters for Pt5 and Pt20 SAXS profiles.

Methods for SAXS data analysis:

Models used: Schulz distribution for the size distribution for spherical particles and Sticky Hard Sphere structure factor (SHS)

The stickiness, τB, is related to the square-well parameters by:

$$\tau_B = (\lambda \exp(-\varepsilon/k_BT))/(12(\lambda-1))$$

where λ and ε describe the relative extension and depth of the square-well, respectively.

Pt20 SAXS profiles needed to be fitted with two structure factors in which that one with the large hard sphere interaction radius is the real structure factor and that one with the unphysical small radius (4 nm) was required to attribute to the non-spherical shape of the particles. Fits using an elliptical form factor with size distribution were not successful.

	Pt5	Pt5 PC	Pt20	Pt20 PC
background	0	0	0.14	0.19
Intensity sphere 1	11725	2569	98145	28278
Radius sphere 1	3.2	2.23	8.3	8.3
σ, sphere 1	0.8	0.9	1.2	1.2
Intensity sphere 2			59.7	21.11
Radius sphere 2			1.44	1.4
σ, sphere 2			0.16	0.16
Radius SHS SF 1	2.7	3.2	0.96	0.97
Vol. fraction SHS SF 1	0.097	0.02	0.39	0.4
λ 1	0.5	0.28	0.91	0.9
ε 1	0.9	5.9	0.99	1.1
Radius SHS SF 2			3.8	4.4
Vol. fraction SHS SF 2			0.0018	0.003
λ 2			1.17	0.87
ε 2			9.7	12.1
Radius SHS SF 3			7.25	9.7
Vol. fraction SHS SF 3			0.02	0.057
λ 3			1.4	0.75
ε 3			0.26	0.6

Table S2. Apparent K_m and V_{max} values of Pt NPs with H_2O_2 and TMB as substrates.

Pt NPs	substrate	K_m (mM)	V_{max} (Ms^{-1})
Pt5	H_2O_2	47.2	1.7E-07
Pt20	H_2O_2	123.6	5.1E-08
Pt5	TMB	11.4	3.5E-06
Pt20	TMB	1.3	1.4E-07

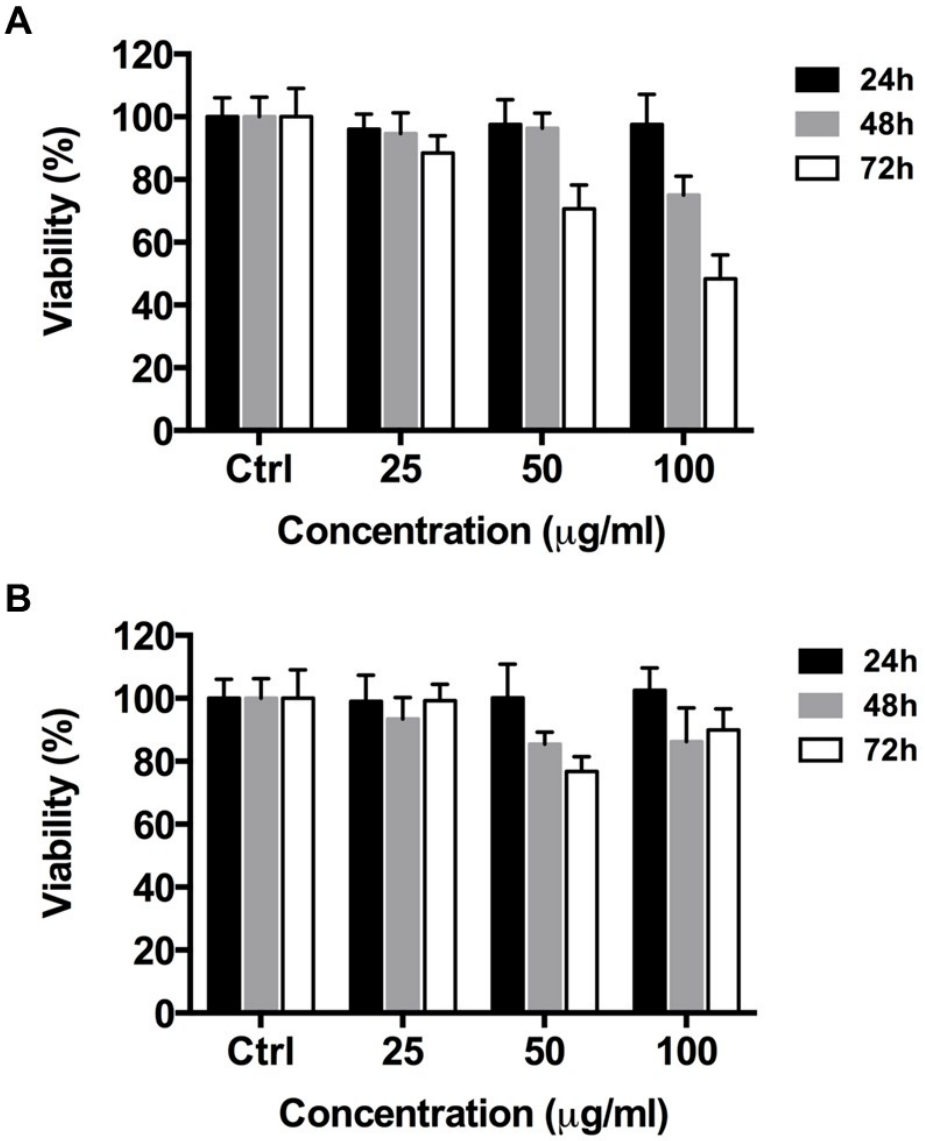

Fig. S9. Viability of MEF *krit1-ko* cells exposed for 24, 48, and 72 hours to increasing doses of Pt5 **(A)** and Pt20 **(B)**. Viability of NPs-treated cells is expressed as relative to untreated control cells (Ctrl). Data are reported as mean ± SD. The experiments were independently performed at least three times.

Supplementary Movie 1. 3D electron tomography reconstruction and the resultant 3D model of a late endosome/lysosome hybrid containing 5 nm Pt NPs. Endosomal membranes, multilamellar bodies, endosomal vesicles and Pt NPs are pseudo-colored respectively in green, cyan, violet, and yellow.

Supplementary Movie 2. 3D electron tomography reconstruction and the resultant 3D model of a late endosome/lysosome hybrid containing 20 nm Pt NPs. Endosomal membranes, multilamellar bodies, endosomal vesicles and Pt NPs are pseudo-colored respectively in green, cyan, violet and yellow.