**Supplementary Information**

**ROS scavenging by IPC-SPIOs at specific regions in the cell**

Comment [cn]: In response to flow cytometry comment. CellROX assay to further validate ROS scavenging

Apart from the DCFDA assay, ROS scavenging was also investigated in macrophages using CellROX (Thermo Fisher Scientific™). Specific CellROX assay dyes were used to detect ROS scavenging at the extracellular membrane, intracellular membrane, and mitochondria. Rapid ROS decline was detected at the extracellular membrane although ROS levels recovered after 2 hours (Fig. S1A). Cell membrane ROS appeared most affected by IPC-SPIOs activity. ROS levels at the cell membrane remained suppressed for the entire 6 hours investigated (Fig. S1B). However, cell membrane ROS appeared to be recovering after 6 hours. Mitochondrial ROS remained in the positive territory and did not decline during the 6 hours investigated (Fig. S1C). Though it should be noted that ROS levels in the mitochondria was almost neutral and barely increased throughout the experiment. Percent change in cellular ROS relative to time 0 hour showed that both extracellular and cell membrane ROS increased relative to time 0 hour with extracellular ROS showing the highest increase (Fig. S1D &E). Significant ROS decline occurred between time 0 hour and 2 hours at the mitochondria, while lesser decline was detected after 6 hours (Fig. S1F). These results complement DCFDA assay by reaffirming IPC-SPIOs' ability to scavenge cellular ROS.

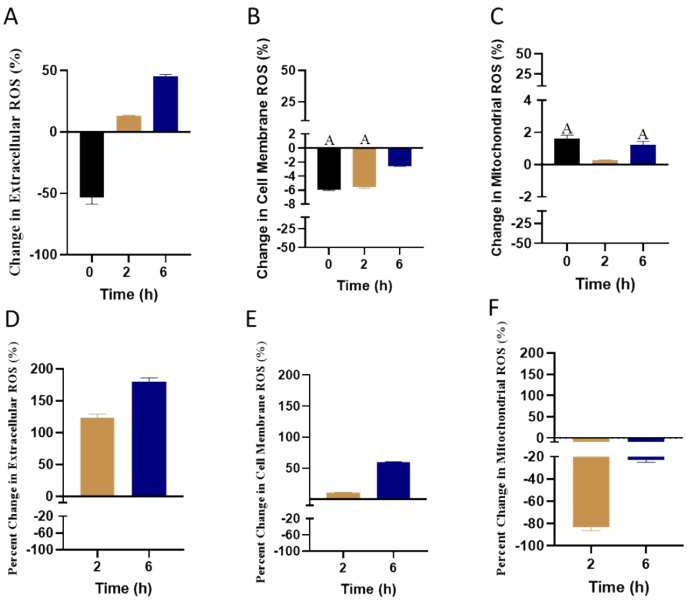


**Figure S1.** Macrophages exposed to 150 µg/mL of IPC-SPIOs. ROS scavenging was detected in the **(A)** extracellular membrane, **(B)** cell membrane, and **(C)** mitochondria over 6 hours using the CellROX assay. **(D)** extracellular, **(E)** cell membrane, and **(F)** mitochondrial percent change

in cellular relative to time 0 hour. Values are shown as mean ± standard deviation. Data were analyzed by a two-way ANOVA and Tukey post-hoc (*P < 0.05, **P < 0.01, # P < 0.001, ## P< 0.0001). Data that do not share any letters are statistically significantly different. n=4

**Comment [cn]:** In response to flow cytometry comment. MRI data to further validate ROS scavenging

**Cellular ROS triggers IPC-SPIOs $T_2$ MRI contrast**

Having established ROS scavenging using fluorescent DCFDA and CellROX, cellular ROS activation of MR signals was investigated using a Philips 3T Achieva Stream MR scanner (Philips; Amsterdam, Netherlands). Macrophages were treated with PEG SPIOs, IPC-SPIOs, or cell media. After 6 hours, $T_2$ MR scans were obtained to investigate cellular ROS-mediated IPC-SPIOs activation. MR contrast was detected in cells treated with IPC-SPIOs and PEG-SPIOs compared to cells treated with media alone (Fig. S2A). Complexed IPC-SPIOs exposed to cells also had a lower $T_2$ value compared to complexed IPC-SPIOs in water (Fig S2B). These results suggest that complexed IPC-SPIOs were decomplexed by cellular ROS to activate shielded $T_2$ MR signals. As expected, PEG SPIOs in water had the shortest $T_2$ compared to other conditions; PEG SPIOs are established $T_2$ contrast agents with very short $T_2$ values. The addition of poly(gallol) increases the $T_2$ values significantly, thereby shielding the contrasting ability of SPIOs. Cellular ROS can reverse the shielding process although not completely, by disrupting the hydrogen bond between PEG and poly(gallol). Disruptions to the hydrogen bond reduces the $T_2$ value and moves those values closer to the original $T_2$ value of PEG SPIOs.

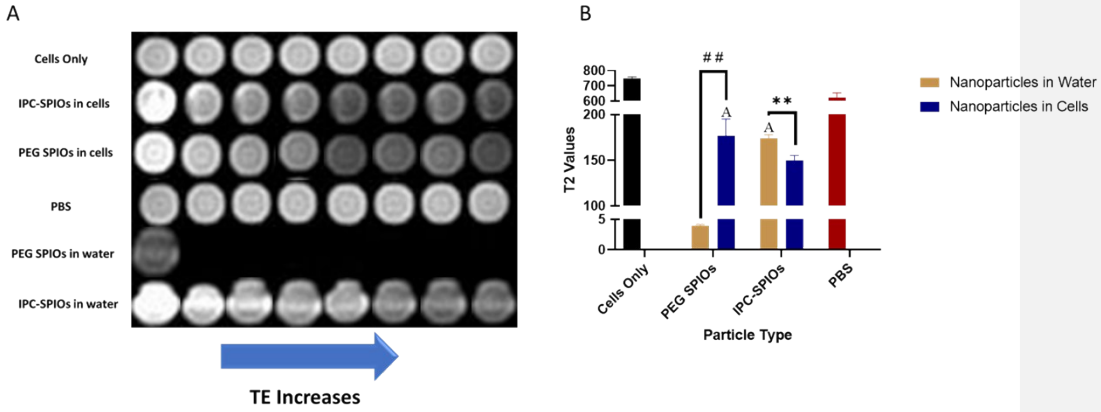


**Figure S2. (A)** $T_2$ – weighted MR images of cells, cells treated with nanoparticles, and nanoparticles in water. **(B)** Representation of $T_2$ values obtained from MR scans for cells, cells treated with nanoparticles, and nanoparticles in water.

**Comparing the ROS scavenging capabilities of IPC-SPIOs over time**

To understand the statistical relationship between ROS scavenging and time, scavenging detected in macrophages, monocytes, and HUVEC were analyzed using Tukey post-hoc test. Here, ROS scavenging detected at a given time point is compared to scavenging at all other time for each cell type by obtaining the p-value of the time points being compared. All cell types showed a statistically significant difference between time 0 h and subsequent timepoints. However, ROS scavenging between 1 – 24 hours was statistically insignificant for most concentrations in macrophages and HUVEC (Fig S3A-C, G-I). Monocytes, on the other hand, experienced statistically significant changes in ROS over 24 hours (Fig S3D-F). These changes were most prominent in cells treated with 100 µg/mL and 150 µg/mL of IPC-SPIOs.

**(a). Macrophages exposed to 75 µg/mL of IPC-SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **1** | <0.0001 | 1 | >0.9999 | >0.9999 | 0.9988 | 0.9973 | >0.9999 | >0.9999 | >0.9999 |
| **2** | <0.0001 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | <0.0001 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | <0.0001 | 0.9988 | >0.9999 | >0.9999 | 1 | >0.9999 | 0.999 | >0.9999 | >0.9999 |
| **12** | <0.0001 | 0.9973 | >0.9999 | >0.9999 | >0.9999 | 1 | 0.9977 | >0.9999 | >0.9999 |
| **16** | <0.0001 | >0.9999 | >0.9999 | >0.9999 | 0.999 | 0.9977 | 1 | >0.9999 | >0.9999 |
| **20** | <0.0001 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | <0.0001 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(b). Macrophages exposed to 100 µg/mL of IPC-SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **1** | <0.0001 | 1 | 0.982 | 0.8704 | 0.4865 | 0.0814 | 0.6242 | 0.5635 | 0.3848 |
| **2** | <0.0001 | 0.982 | 1 | >0.9999 | 0.9778 | 0.567 | 0.9944 | 0.9892 | 0.9494 |
| **4** | <0.0001 | 0.8704 | >0.9999 | 1 | 0.9994 | 0.8331 | >0.9999 | 0.9999 | 0.9969 |
| **8** | <0.0001 | 0.4865 | 0.9778 | 0.9994 | 1 | 0.9919 | >0.9999 | >0.9999 | >0.9999 |
| **12** | <0.0001 | 0.0814 | 0.567 | 0.8331 | 0.9919 | 1 | 0.9707 | 0.9825 | 0.9978 |
| **16** | <0.0001 | 0.6242 | 0.9944 | >0.9999 | >0.9999 | 0.9707 | 1 | >0.9999 | >0.9999 |
| **20** | <0.0001 | 0.5635 | 0.9892 | 0.9999 | >0.9999 | 0.9825 | >0.9999 | 1 | >0.9999 |
| **24** | <0.0001 | 0.3848 | 0.9494 | 0.9969 | >0.9999 | 0.9978 | >0.9999 | >0.9999 | 1 |

**(c). Macrophages exposed to 150 µg/mL of IPC-SPIOs over 24 hours**

| Time (h) | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.9083 | 0.0136 | 0.002 | 0.0006 | 0.0005 | 0.3795 | 0.4348 | 0.327 |
| **1** | 0.9083 | 1 | 0.3697 | 0.1154 | 0.0475 | 0.0445 | 0.9926 | 0.9964 | 0.9863 |
| **2** | 0.0136 | 0.3697 | 1 | 0.9997 | 0.9904 | 0.9887 | 0.9025 | 0.8672 | 0.9316 |
| **4** | 0.002 | 0.1154 | 0.9997 | 1 | >0.9999 | >0.9999 | 0.5746 | 0.5148 | 0.635 |
| **8** | 0.0006 | 0.0475 | 0.9904 | >0.9999 | 1 | >0.9999 | 0.3484 | 0.299 | 0.4025 |
| **12** | 0.0005 | 0.0445 | 0.9887 | >0.9999 | >0.9999 | 1 | 0.3343 | 0.2861 | 0.3874 |
| **16** | 0.3795 | 0.9926 | 0.9025 | 0.5746 | 0.3484 | 0.3343 | 1 | >0.9999 | >0.9999 |
| **20** | 0.4348 | 0.9964 | 0.8672 | 0.5148 | 0.299 | 0.2861 | >0.9999 | 1 | >0.9999 |
| **24** | 0.327 | 0.9863 | 0.9316 | 0.635 | 0.4025 | 0.3874 | >0.9999 | >0.9999 | 1 |

**(d). Monocytes exposed to 75 µg/mL of IPC-SPIOs over 24 hours**

| Time (h) | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.4442 | >0.9999 | 0.9997 | 0.785 | 0.597 | 0.9886 | >0.9999 | >0.9999 |
| **1** | 0.4442 | 1 | 0.4484 | 0.154 | 0.0085 | 0.0032 | 0.9546 | 0.6253 | 0.5908 |
| **2** | >0.9999 | 0.4484 | 1 | 0.9997 | 0.7813 | 0.5927 | 0.9891 | >0.9999 | >0.9999 |
| **4** | 0.9997 | 0.154 | 0.9997 | 1 | 0.9786 | 0.9115 | 0.8374 | 0.9951 | 0.9968 |
| **8** | 0.785 | 0.0085 | 0.7813 | 0.9786 | 1 | >0.9999 | 0.2079 | 0.6153 | 0.6495 |
| **12** | 0.597 | 0.0032 | 0.5927 | 0.9115 | >0.9999 | 1 | 0.1079 | 0.4173 | 0.4502 |
| **16** | 0.9886 | 0.9546 | 0.9891 | 0.8374 | 0.2079 | 0.1079 | 1 | 0.9988 | 0.998 |
| **20** | >0.9999 | 0.6253 | >0.9999 | 0.9951 | 0.6153 | 0.4173 | 0.9988 | 1 | >0.9999 |
| **24** | >0.9999 | 0.5908 | >0.9999 | 0.9968 | 0.6495 | 0.4502 | 0.998 | >0.9999 | 1 |

**(e). Monocytes exposed to 100 µg/mL of IPC-SPIOs over 24 hours**

| Time (h) | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.8784 | 0.4696 | 0.0987 | 0.0006 | 0.0004 | >0.9999 | 0.9093 | 0.8202 |
| **1** | 0.8784 | 1 | 0.0173 | 0.0012 | <0.0001 | <0.0001 | 0.7648 | 0.1313 | 0.0801 |
| **2** | 0.4696 | 0.0173 | 1 | 0.9964 | 0.2723 | 0.2318 | 0.6216 | 0.9977 | 0.9998 |
| **4** | 0.0987 | 0.0012 | 0.9964 | 1 | 0.7772 | 0.7272 | 0.1656 | 0.8221 | 0.9105 |
| **8** | 0.0006 | <0.0001 | 0.2723 | 0.7772 | 1 | >0.9999 | 0.0013 | 0.0474 | 0.0812 |
| **12** | 0.0004 | <0.0001 | 0.2318 | 0.7272 | >0.9999 | 1 | 0.001 | 0.0376 | 0.0655 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **16** | >0.9999 | 0.7648 | 0.6216 | 0.1656 | 0.0013 | 0.001 | 1 | 0.9671 | 0.9159 |
| **20** | 0.9093 | 0.1313 | 0.9977 | 0.8221 | 0.0474 | 0.0376 | 0.9671 | 1 | >0.9999 |
| **24** | 0.8202 | 0.0801 | 0.9998 | 0.9105 | 0.0812 | 0.0655 | 0.9159 | >0.9999 | 1 |

**(f). Monocytes exposed to 150 µg/mL of IPC-SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.9615 | 0.0002 | <0.0001 | <0.0001 | <0.0001 | 0.0521 | 0.0155 | 0.0095 |
| **1** | 0.9615 | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0013 | 0.0003 | 0.0002 |
| **2** | 0.0002 | <0.0001 | 1 | 0.3747 | 0.0011 | 0.0004 | 0.7912 | 0.9546 | 0.9807 |
| **4** | <0.0001 | <0.0001 | 0.3747 | 1 | 0.4691 | 0.2944 | 0.0061 | 0.0229 | 0.0361 |
| **8** | <0.0001 | <0.0001 | 0.0011 | 0.4691 | 1 | >0.9999 | <0.0001 | <0.0001 | <0.0001 |
| **12** | <0.0001 | <0.0001 | 0.0004 | 0.2944 | >0.9999 | 1 | <0.0001 | <0.0001 | <0.0001 |
| **16** | 0.0521 | 0.0013 | 0.7912 | 0.0061 | <0.0001 | <0.0001 | 1 | >0.9999 | 0.9997 |
| **20** | 0.0155 | 0.0003 | 0.9546 | 0.0229 | <0.0001 | <0.0001 | >0.9999 | 1 | >0.9999 |
| **24** | 0.0095 | 0.0002 | 0.9807 | 0.0361 | <0.0001 | <0.0001 | 0.9997 | >0.9999 | 1 |

**(g). HUVEC exposed to 75 µg/mL of IPC-SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.5649 | 0.0962 | 0.0273 | 0.0035 | 0.0028 | 0.0357 | 0.0413 | 0.0305 |
| **1** | 0.5649 | 1 | 0.9886 | 0.8835 | 0.4913 | 0.4509 | 0.9178 | 0.9337 | 0.8984 |
| **2** | 0.0962 | 0.9886 | 1 | >0.9999 | 0.9684 | 0.9569 | >0.9999 | >0.9999 | >0.9999 |
| **4** | 0.0273 | 0.8835 | >0.9999 | 1 | 0.9992 | 0.9984 | >0.9999 | >0.9999 | >0.9999 |
| **8** | 0.0035 | 0.4913 | 0.9684 | 0.9992 | 1 | >0.9999 | 0.9978 | 0.9965 | 0.9987 |
| **12** | 0.0028 | 0.4509 | 0.9569 | 0.9984 | >0.9999 | 1 | 0.9963 | 0.9943 | 0.9977 |
| **16** | 0.0357 | 0.9178 | >0.9999 | >0.9999 | 0.9978 | 0.9963 | 1 | >0.9999 | >0.9999 |
| **20** | 0.0413 | 0.9337 | >0.9999 | >0.9999 | 0.9965 | 0.9943 | >0.9999 | 1 | >0.9999 |
| **24** | 0.0305 | 0.8984 | >0.9999 | >0.9999 | 0.9987 | 0.9977 | >0.9999 | >0.9999 | 1 |

**(h). HUVEC exposed to 100 µg/mL of IPC-SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **1** | <0.0001 | 1 | 0.7303 | 0.5099 | 0.4212 | 0.4607 | 0.9885 | 0.9958 | 0.992 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **2** | <0.0001 | 0.7303 | 1 | >0.9999 | >0.9999 | >0.9999 | 0.9975 | 0.9924 | 0.9961 |
| **4** | <0.0001 | 0.5099 | >0.9999 | 1 | >0.9999 | >0.9999 | 0.9729 | 0.9467 | 0.9645 |
| **8** | <0.0001 | 0.4212 | >0.9999 | >0.9999 | 1 | >0.9999 | 0.9466 | 0.9064 | 0.9332 |
| **12** | <0.0001 | 0.4607 | >0.9999 | >0.9999 | >0.9999 | 1 | 0.9601 | 0.9265 | 0.9491 |
| **16** | <0.0001 | 0.9885 | 0.9975 | 0.9729 | 0.9466 | 0.9601 | 1 | >0.9999 | >0.9999 |
| **20** | <0.0001 | 0.9958 | 0.9924 | 0.9467 | 0.9064 | 0.9265 | >0.9999 | 1 | >0.9999 |
| **24** | <0.0001 | 0.992 | 0.9961 | 0.9645 | 0.9332 | 0.9491 | >0.9999 | >0.9999 | 1 |

**(i). HUVEC exposed to 150 µg/mL of IPC-SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **1** | <0.0001 | 1 | 0.7437 | 0.7169 | 0.6939 | 0.6912 | >0.9999 | >0.9999 | 0.9999 |
| **2** | <0.0001 | 0.7437 | 1 | >0.9999 | >0.9999 | >0.9999 | 0.9503 | 0.9316 | 0.9554 |
| **4** | <0.0001 | 0.7169 | >0.9999 | 1 | >0.9999 | >0.9999 | 0.9395 | 0.9183 | 0.9453 |
| **8** | <0.0001 | 0.6939 | >0.9999 | >0.9999 | 1 | >0.9999 | 0.9293 | 0.9059 | 0.9358 |
| **12** | <0.0001 | 0.6912 | >0.9999 | >0.9999 | >0.9999 | 1 | 0.9281 | 0.9044 | 0.9346 |
| **16** | <0.0001 | >0.9999 | 0.9503 | 0.9395 | 0.9293 | 0.9281 | 1 | >0.9999 | >0.9999 |
| **20** | <0.0001 | >0.9999 | 0.9316 | 0.9183 | 0.9059 | 0.9044 | >0.9999 | 1 | >0.9999 |
| **24** | <0.0001 | 0.9999 | 0.9554 | 0.9453 | 0.9358 | 0.9346 | >0.9999 | >0.9999 | 1 |

**Fig. S3** P-values obtained by comparing ROS scavenging by IPC-SPIOs at every time point for 24 hours in **(A)** Macrophages treated with 75 µg/mL, **(B)** Macrophages treated with 100 µg/mL, **(C)** Macrophages treated with 150 µg/mL, **(D)** Monocytes treated with 75 µg/mL, **(E)** Monocytes treated with 100 µg/mL, **(F)** Monocytes treated with 150 µg/mL, **(G)** HUVEC treated with 75 µg/mL, **(H)** HUVEC treated with 100 µg/mL, and **(i)** HUVEC treated with 150 µg/mL. Data were analyzed by a one-way ANOVA and Tukey's post-hoc test. n=4

**Comparing the antioxidant effects of PEG SPIOs over time**

Like ROS scavenging, the statistical relationship between antioxidant effects of PEG SPIOs and time was also investigated in macrophages, monocytes, and HUVEC using Tukey post-hoc test. Antioxidant action at a given time point is compared to scavenging at all other time for each cell type by obtaining the p-value of the time points being compared. The antioxidant effects of PEG

SPIOs were mostly statistically similar over 24 hours. Monocytes did not experience any statistically significant changes in ROS over 24 hours as PEG SPIOs had the same effect on cells (Fig S4D-F). In macrophages, cellular ROS was the same in cells treated with 75 and 100 µg/mL of PEG SPIOs; however, the effect of PEG SPIOs was detected in cells 150 µg/mL from 2-24 hours (Fig S4A-C). HUVEC was the only cell line to show statistically significant ROS reduction at two different concentrations. ROS reduction was observed at 100 and 150 µg/mL at 0 hour (Fig S4G-I).

**(a). Macrophages exposed to 75 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | >0.9999 | 0.9996 | 0.9995 | 0.9991 | 0.9996 | >0.9999 | >0.9999 | >0.9999 |
| **1** | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **2** | 0.9996 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | 0.9995 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | 0.9991 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **12** | 0.9996 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 |
| **16** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 |
| **20** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(b). Macrophages exposed to 100 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.9235 | 0.7132 | 0.6859 | 0.5293 | 0.5492 | 0.745 | 0.7984 | 0.7123 |
| **1** | 0.9235 | 1 | >0.9999 | >0.9999 | 0.9985 | 0.9989 | >0.9999 | >0.9999 | >0.9999 |
| **2** | 0.7132 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | 0.6859 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | 0.5293 | 0.9985 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **12** | 0.5492 | 0.9989 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 |
| **16** | 0.745 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **20** | 0.7984 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | 0.7123 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(c). Macrophages exposed to 150 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.3596 | 0.0237 | 0.0095 | 0.0036 | 0.0041 | 0.044 | 0.0578 | 0.0451 |
| **1** | 0.3596 | 1 | 0.9622 | 0.8702 | 0.7087 | 0.7351 | 0.9896 | 0.9951 | 0.9903 |
| **2** | 0.0237 | 0.9622 | 1 | >0.9999 | 0.9996 | 0.9998 | >0.9999 | >0.9999 | >0.9999 |
| **4** | 0.0095 | 0.8702 | >0.9999 | 1 | >0.9999 | >0.9999 | 0.9999 | 0.9995 | 0.9998 |
| **8** | 0.0036 | 0.7087 | 0.9996 | >0.9999 | 1 | >0.9999 | 0.9961 | 0.9914 | 0.9958 |
| **12** | 0.0041 | 0.7351 | 0.9998 | >0.9999 | >0.9999 | 1 | 0.9973 | 0.9937 | 0.9971 |
| **16** | 0.044 | 0.9896 | >0.9999 | 0.9999 | 0.9961 | 0.9973 | 1 | >0.9999 | >0.9999 |
| **20** | 0.0578 | 0.9951 | >0.9999 | 0.9995 | 0.9914 | 0.9937 | >0.9999 | 1 | >0.9999 |
| **24** | 0.0451 | 0.9903 | >0.9999 | 0.9998 | 0.9958 | 0.9971 | >0.9999 | >0.9999 | 1 |

**(d). Monocytes exposed to 75 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **1** | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | 0.9998 | >0.9999 | >0.9999 | >0.9999 |
| **2** | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **12** | >0.9999 | 0.9998 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 |
| **16** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 |
| **20** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(e). Monocytes exposed to 100 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **1** | >0.9999 | 1 | >0.9999 | >0.9999 | 0.9996 | 0.9991 | >0.9999 | 0.9998 | 0.9997 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **2** | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | >0.9999 | 0.9996 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **12** | >0.9999 | 0.9991 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 |
| **16** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 |
| **20** | >0.9999 | 0.9998 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | >0.9999 | 0.9997 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(f). Monocytes exposed to 150 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | >0.9999 | >0.9999 | >0.9999 | 0.9985 | 0.9975 | >0.9999 | >0.9999 | >0.9999 |
| **1** | >0.9999 | 1 | 0.9998 | 0.9994 | 0.9899 | 0.9854 | >0.9999 | >0.9999 | 0.9998 |
| **2** | >0.9999 | 0.9998 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | >0.9999 | 0.9994 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | 0.9985 | 0.9899 | >0.9999 | >0.9999 | 1 | >0.9999 | 0.9997 | >0.9999 | >0.9999 |
| **12** | 0.9975 | 0.9854 | >0.9999 | >0.9999 | >0.9999 | 1 | 0.9993 | 0.9999 | >0.9999 |
| **16** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 0.9997 | 0.9993 | 1 | >0.9999 | >0.9999 |
| **20** | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | >0.9999 | 0.9998 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(g). HUVEC exposed to 75 µg/mL of PEG SPIOs over 24 hours**

| **Time (h)** | **0** | **1** | **2** | **4** | **8** | **12** | **16** | **20** | **24** |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.2268 | 0.1276 | 0.1208 | 0.106 | 0.1302 | 0.2036 | 0.2471 | 0.1841 |
| **1** | 0.2268 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **2** | 0.1276 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | 0.1208 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | 0.106 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **12** | 0.1302 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 |
| **16** | 0.2036 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 |
| **20** | 0.2471 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | 0.1841 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(h). HUVEC exposed to 100 µg/mL of PEG SPIOs over 24 hours**

| Time (h) | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | 0.0014 | 0.0002 | 0.0002 | <0.0001 | <0.0001 | 0.0002 | 0.0004 | 0.0002 |
| **1** | 0.0014 | 1 | 0.9998 | 0.9995 | 0.9924 | 0.9943 | >0.9999 | >0.9999 | 0.9998 |
| **2** | 0.0002 | 0.9998 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **4** | 0.0002 | 0.9995 | >0.9999 | 1 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 |
| **8** | <0.0001 | 0.9924 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 | 0.9998 | >0.9999 |
| **12** | <0.0001 | 0.9943 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | 0.9999 | >0.9999 |
| **16** | 0.0002 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 | >0.9999 | >0.9999 |
| **20** | 0.0004 | >0.9999 | >0.9999 | >0.9999 | 0.9998 | 0.9999 | >0.9999 | 1 | >0.9999 |
| **24** | 0.0002 | 0.9998 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | >0.9999 | 1 |

**(i). HUVEC exposed to 150 µg/mL of PEG SPIOs over 24 hours**

| Time (h) | 0 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **1** | <0.0001 | 1 | 0.866 | 0.6505 | 0.3998 | 0.4339 | 0.9556 | 0.9775 | 0.9581 |
| **2** | <0.0001 | 0.866 | 1 | >0.9999 | 0.9977 | 0.9986 | >0.9999 | >0.9999 | >0.9999 |
| **4** | <0.0001 | 0.6505 | >0.9999 | 1 | >0.9999 | >0.9999 | 0.9992 | 0.9971 | 0.9991 |
| **8** | <0.0001 | 0.3998 | 0.9977 | >0.9999 | 1 | >0.9999 | 0.9816 | 0.9625 | 0.9802 |
| **12** | <0.0001 | 0.4339 | 0.9986 | >0.9999 | >0.9999 | 1 | 0.9869 | 0.9717 | 0.9859 |
| **16** | <0.0001 | 0.9556 | >0.9999 | 0.9992 | 0.9816 | 0.9869 | 1 | >0.9999 | >0.9999 |
| **20** | <0.0001 | 0.9775 | >0.9999 | 0.9971 | 0.9625 | 0.9717 | >0.9999 | 1 | >0.9999 |
| **24** | <0.0001 | 0.9581 | >0.9999 | 0.9991 | 0.9802 | 0.9859 | >0.9999 | >0.9999 | 1 |

**Fig. S4** P-values obtained by comparing PEG SPIOs antioxidant effect at every time point for 24 hours in **(A)** Macrophages treated with 75 µg/mL **(B)** Macrophages treated with 100 µg/mL **(C)** Macrophages treated with 150 µg/mL **(D)** Monocytes treated with 75 µg/mL **(E)** Monocytes treated with 100 µg/mL **(F)** Monocytes treated with 150 µg/mL **(G)** HUVEC treated with 75 µg/mL **(H)** HUVEC treated with 100 µg/mL **(I)** HUVEC treated with 150 µg/mL. Data were analyzed by a one-way ANOVA and Tukey's post-hoc test. n=4

**IPC-SPIOS rate of ROS scavenging**

Rate of ROS scavenging was also investigated to determine if the interaction of IPC-SPIOs with ROS changes over time. In macrophages, scavenging does not appear to follow any trends. The rate of scavenging alternated with between concentrations over 24 hours (Fig S3a). For HUVEC, ROS scavenging appears to be mostly concentration dependent as the lowest concentration induced the highest rate of ROS scavenging over time (Fig S3b). Interestingly, IPC-SPIOs followed the same scavenging pattern regardless of concentration in monocytes. Apart from 12 hours and 20 hours, rate of scavenging was mostly the same for each concentration at most timepoints (Fig S3c).

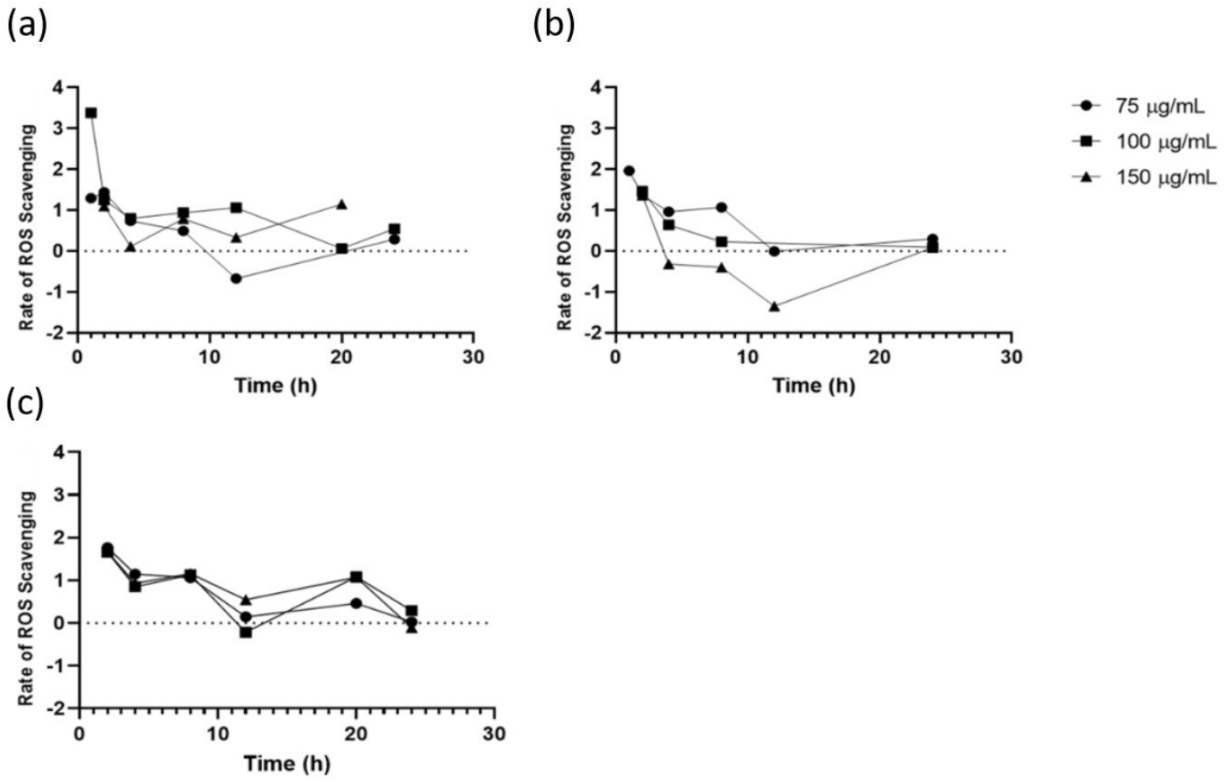


**Fig. S5** Rate of ROS scavenging by IPC-SPIOs over 24 hours (data represented as log base 10) **(A)** Macrophages, **(B)** HUVEC, and **(C)** Monocytes n=4

**DCFDA ROS Data**

**Comment [cn]:** In response inclusion of data comment

### (A) Macrophages

| Time (h) | Cells Only | PEG 75 | Error | PEG 100 | Error | PEG 150 | Error | IPC 75 | Error | IPC 100 | Error | IPC 150 | Error |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 26498 | 29371 | 13714.35 | 34490 | 19470.77 | 29280 | 13671.86 | 32123 | 3086.764 | 26104 | 6520.596 | 14658 | 2733.824 |
| 1 | 32868 | 26584 | 429.3494 | 27124 | 677.2483 | 22377 | 361.4035 | 25955 | 1577.383 | 20577 | 1833.934 | 15266 | 1369.849 |
| 2 | 27030 | 22216 | 372.1627 | 22043 | 590.9237 | 16681 | 279.4403 | 20621 | 1071.123 | 15113 | 1521.228 | 8552 | 727.9715 |
| 4 | 27909 | 23000 | 311.768 | 22453 | 468.7895 | 17169 | 232.728 | 21205 | 1082.919 | 14820 | 1579.47 | 7773 | 749.7057 |
| 8 | 33294 | 27210 | 285.7213 | 26580 | 501.9248 | 19184 | 201.4435 | 24801 | 1172.38 | 16311 | 1192.855 | 8515 | 809.245 |
| 12 | 36430 | 29892 | 392.9459 | 29096 | 564.9515 | 20786 | 273.2428 | 26936 | 1556.308 | 15692 | 1022.262 | 9259 | 989.2779 |
| 16 | 38448 | 32745 | 387.3504 | 32297 | 617.2079 | 25621 | 303.0785 | 30316 | 1669.655 | 19346 | 1042.398 | 15616 | 798.5852 |
| 20 | 40029 | 34090 | 423.3116 | 33124 | 615.1786 | 25799 | 320.3583 | 30356 | 1569.21 | 19908 | 885.8274 | 16488 | 812.8704 |
| 24 | 36122 | 30433 | 402.6928 | 29940 | 619.6535 | 22935 | 303.4784 | 27593 | 1530.074 | 17324 | 819.9619 | 14461 | 773.3013 |

**(B) Monocytes**

| Time (h) | Cells | PEG 75 | Error | PEG 100 | Error | PEG 150 | Error | IPC 75 | Error | IPC 100 | Error | IPC 150 | Error |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 12198.75 | 11493 | 5735.769 | 11364.5 | 6415.644 | 10099 | 5040.071 | 9970.25 | 236.4342 | 9188.75 | 216.2505 | 8448.25 | 205.1908 |
| 1 | 20350.25 | 20006 | 1461.54 | 19722 | 5262.297 | 17509 | 1279.122 | 17817.25 | 274.6506 | 16120.75 | 293.5313 | 14733.75 | 786.1533 |
| 2 | 15145.75 | 14433.25 | 819.0649 | 14076 | 5468.123 | 11865 | 673.3206 | 12381.5 | 309.9295 | 10542.75 | 330.408 | 8529.25 | 716.4178 |
| 4 | 15906.25 | 15045.75 | 592.1852 | 14716.5 | 1443.867 | 12263 | 482.659 | 12753.75 | 309.3167 | 10726.25 | 338.9643 | 7984 | 557.0039 |
| 8 | 19627.75 | 18033.75 | 493.8182 | 17373.5 | 1025.181 | 14271.75 | 390.8033 | 15177.5 | 386.1262 | 12364 | 470.4061 | 8729.5 | 471.6559 |
| 12 | 21727.75 | 19745.5 | 725.9978 | 19002.75 | 763.055 | 15632.25 | 574.7628 | 16627.25 | 411.008 | 13637.5 | 477.047 | 9493.5 | 497.03 |
| 16 | 25812.25 | 24467.75 | 994.9625 | 23481.25 | 885.8954 | 20892.5 | 849.5776 | 21764 | 546.501 | 19286 | 540.8915 | 15665.25 | 578.0864 |
| 20 | 27558.25 | 25791.75 | 510.4641 | 24577.25 | 618.4066 | 21839.5 | 432.2421 | 22724.5 | 525.1177 | 19746.25 | 530.4952 | 16411.25 | 557.5145 |
| 24 | 24646.25 | 22598.75 | 372.5989 | 21858 | 544.9269 | 19328.75 | 318.6845 | 20289.25 | 624.0308 | 17522.75 | 676.2884 | 14571.25 | 640.8818 |

**(C) HUVEC**

| Time (h) | Cells | PEG 75 | Error | PEG 100 | Error | PEG 150 | Error | IPC 75 | Error | IPC 100 | Error | IPC 150 | Error |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 18069.75 | 19815.75 | 9252.671 | 21632 | 3913.266 | 21282.25 | 9937.432 | 14048 | 1289.839 | 19752 | 2793.968 | 26476 | 7266.113 |
| 1 | 55126.5 | 47289.5 | 763.7571 | 42739 | 1067.133 | 31941.25 | 515.8726 | 34990.75 | 1894.95 | 26225.75 | 2129.981 | 19281.5 | 1829.512 |
| 2 | 42938 | 35753.5 | 598.943 | 31073.5 | 833.0112 | 18957.25 | 317.572 | 23585.5 | 1890.923 | 13821 | 1830.593 | 8496.5 | 1478.788 |
| 4 | 43868 | 36430.75 | 493.8236 | 31523 | 658.1593 | 17811.5 | 241.4372 | 22251.25 | 1912.627 | 12818.5 | 1742.788 | 8510 | 1533.849 |
| 8 | 44272.5 | 36537.5 | 383.6657 | 30586.75 | 577.5864 | 16408.75 | 172.3017 | 19866.25 | 1771.031 | 12403 | 1734.77 | 8444.75 | 1586.751 |
| 12 | 44481.75 | 37075.5 | 487.3767 | 30885.75 | 599.7027 | 16711 | 219.6748 | 19716.75 | 1829.323 | 12704 | 1779.138 | 8468.25 | 1615.182 |
| 16 | 58906.75 | 50237.25 | 594.2715 | 42990.5 | 821.5648 | 27534.25 | 325.7109 | 30372.75 | 2034.971 | 22986.75 | 1992.419 | 18058.5 | 1785.321 |
| 20 | 44615 | 38456.25 | 477.5293 | 33051.75 | 613.8368 | 21391.25 | 265.6252 | 23212.5 | 1600.025 | 17946.75 | 1556.563 | 13963.75 | 1385.5 |
| 24 | 45466.25 | 38568.25 | 510.3393 | 32895.25 | 680.8169 | 21302.25 | 281.8737 | 23218 | 1654.607 | 17947.75 | 1620.149 | 13846.25 | 1437.404 |

**Fig. S6** Raw data from nanoparticle interactions with cellular ROS in **(A)** Macrophages, **(B)** HUVEC, and **(C)** Monocytes