Derivation of Membrane and Receptor Mediated Kinetic Model of SWCNT Uptake.

Equation S1 describes reversible SWCNT association with the cell surface, followed by membrane surface internalization. Equation S2 describes reversible SWCNT binding to a surface receptor, followed by internalization of the SWCNT–receptor complex. The model assumes a complete dissociation of internalized SWCNT–receptor complexes and constant total receptor concentration. Equation S3 describes expulsion of internalized SWCNTs back into the extracellular SWCNT reservoir.

$$[SWCNT]_{\text{ext}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SWCNT]_{\text{surf}} \overset{k_2}{\rightarrow} [SWCNT]_{\text{int}} \quad \text{(S1)}$$

$$[SWCNT]_{\text{ext}} + [R] \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [SWCNT-R] \overset{k_4}{\rightarrow} [SWCNT]_{\text{int}} + [R] \quad \text{(S2)}$$

$$[SWCNT]_{\text{int}} \overset{k_5}{\rightarrow} [SWCNT]_{\text{ext}} \quad \text{(S3)}$$

Thus, the rate equations for external SWCNTs, surface associated SWCNTs, SWCNT–receptor complexes, receptors and internalized SWCNTs are given by equations S4 – S8.

$$\frac{d[SWCNT]_{\text{ext}}}{dt} = -k_1[SWCNT]_{\text{ext}} + k_{-1}[SWCNT]_{\text{surf}} - k_3[SWCNT]_{\text{ext}}[R] + k_{-3}[SWCNT-R] + k_5[SWCNT]_{\text{int}} \quad \text{(S4)}$$

$$\frac{d[SWCNT]_{\text{surf}}}{dt} = k_1[SWCNT]_{\text{ext}} - k_{-1}[SWCNT]_{\text{surf}} - k_2[SWCNT]_{\text{surf}} \quad \text{(S5)}$$

$$\frac{d[SWCNT-R]}{dt} = k_3[SWCNT]_{\text{ext}}[R] - k_{-3}[SWCNT-R] - k_4[SWCNT-R] \quad \text{(S6)}$$

$$\frac{d[R]}{dt} = -k_3[SWCNT]_{\text{ext}}[R] + k_{-3}[SWCNT-R] + k_4[SWCNT-R] \quad \text{(S7)}$$

$$\frac{d[SWCNT]_{\text{int}}}{dt} = k_2[SWCNT]_{\text{surf}} + k_4[SWCNT-R] - k_5[SWCNT]_{\text{int}} \quad \text{(S8)}$$

If we assume that the concentration of surface adsorption sites and receptors is much less than external SWCNT concentration, then surface associated SWCNTs and SWCNT–receptor complexes will replenish about as quickly as they are internalized, creating a pseudo-steady state concentration for both species. Thus, rate equations S5 and S6 are approximately equal to zero, and can be used to write expressions for surface associated SWCNT and SWCNT–receptor complexes given by equations S9 and S10 with the condition of equation S11.

$$[SWCNT]_{\text{surf}} = \frac{k_1[SWCNT]_{\text{ext}}}{k_{-1}+k_2} \quad \text{(S9)}$$

$$[SWCNT-R] = \frac{k_3[SWCNT]_{\text{ext}}[R]}{k_{-3}+k_4} \quad \text{(S10)}$$

$$[R]_{TOT} = [R] + [SWCNT-R] \quad \text{(S11)}$$

We also assume the internalized SWCNT concentration has reached steady state value after 48 h. Setting equation S8 equal to zero and solving for internalized SWCNTs results in equation S12.

$$[SWCNT]_{\text{int}} = \frac{k_2}{k_5}[SWCNT]_{\text{surf}} + \frac{k_4}{k_5}[SWCNT-R] \quad \text{(S12)}$$

Along with a total receptor balance, given by equation S11, equations S9 and S10 can be substituted into equation S12 to arrive at the steady state intracellular SWCNT concentration represented for SWCNT–PF127 uptake in equation S13 (rewritten as S14) and SWCNT–BSA uptake in equation S15 (rewritten as S16). Equation S14 is equivalent to equation 1 of the text, and equation S16 is equivalent to equation 4 of the text.

$$[SWCNT]_{\text{int}} = \left(\frac{k_2}{k_5}\right)\left(\frac{k_1}{k_{-1}+k_2}\right)[SWCNT]_{\text{ext}} \quad \text{(S13)}$$

$$[SWCNT]_{\text{int}} = K_{\text{mem}}[SWCNT]_{\text{ext}} \quad \text{(S14)}$$

$$[SWCNT]_{\text{int}} = \left(\frac{k_2}{k_5}\right)\left(\frac{k_1}{k_{-1}+k_2}\right)[SWCNT]_{\text{ext}} + \left(\frac{k_4}{k_5}\right)\frac{k_4[R]_{TOT}[SWCNT]_{\text{ext}}}{\left(\frac{k_{-3}+k_4}{k_{-3}}\right)+[SWCNT]_{\text{ext}}} \quad \text{(S15)}$$

$$[SWCNT]_{\text{int}} = K_{\text{mem}}[SWCNT]_{\text{ext}} + \frac{\alpha[SWCNT]_{\text{ext}}}{\beta+[SWCNT]_{\text{ext}}} \quad \text{(S16)}$$

Parameter fitting

K'_{mem} was imputed to the model as a constant, and the resulting best overall fit shown in Figure 4 was achieved with parameters α and β equal to ~21 pg/cell and ~4 μg/mL, respectively. In the limit of high $[SWCNT]_{\text{ext}} \geq 10$ μg/mL, $[SWCNT]_{\text{int}} \sim \alpha + K'_{\text{mem}}[SWCNT]_{\text{ext}}$ and linear regression of the data taking $K'_{\text{mem}} = 0.492$ resulted in $\alpha = 18 \pm 5$ pg/cell. In the limit of low $[SWCNT]_{\text{ext}} \leq 10$ μg/mL, $[SWCNT]_{\text{int}} \sim (\alpha/\beta + K'_{\text{mem}})[SWCNT]_{\text{ext}}$ and linear regression of the data taking $K'_{\text{mem}} = 0.492$ and $\alpha = 18 \pm 5$ pg/cell resulted in $\beta = 10 \pm 7$ μg/mL, where the uncertainty in β was obtained through propagation of uncertain in α.

Supplemental Figures

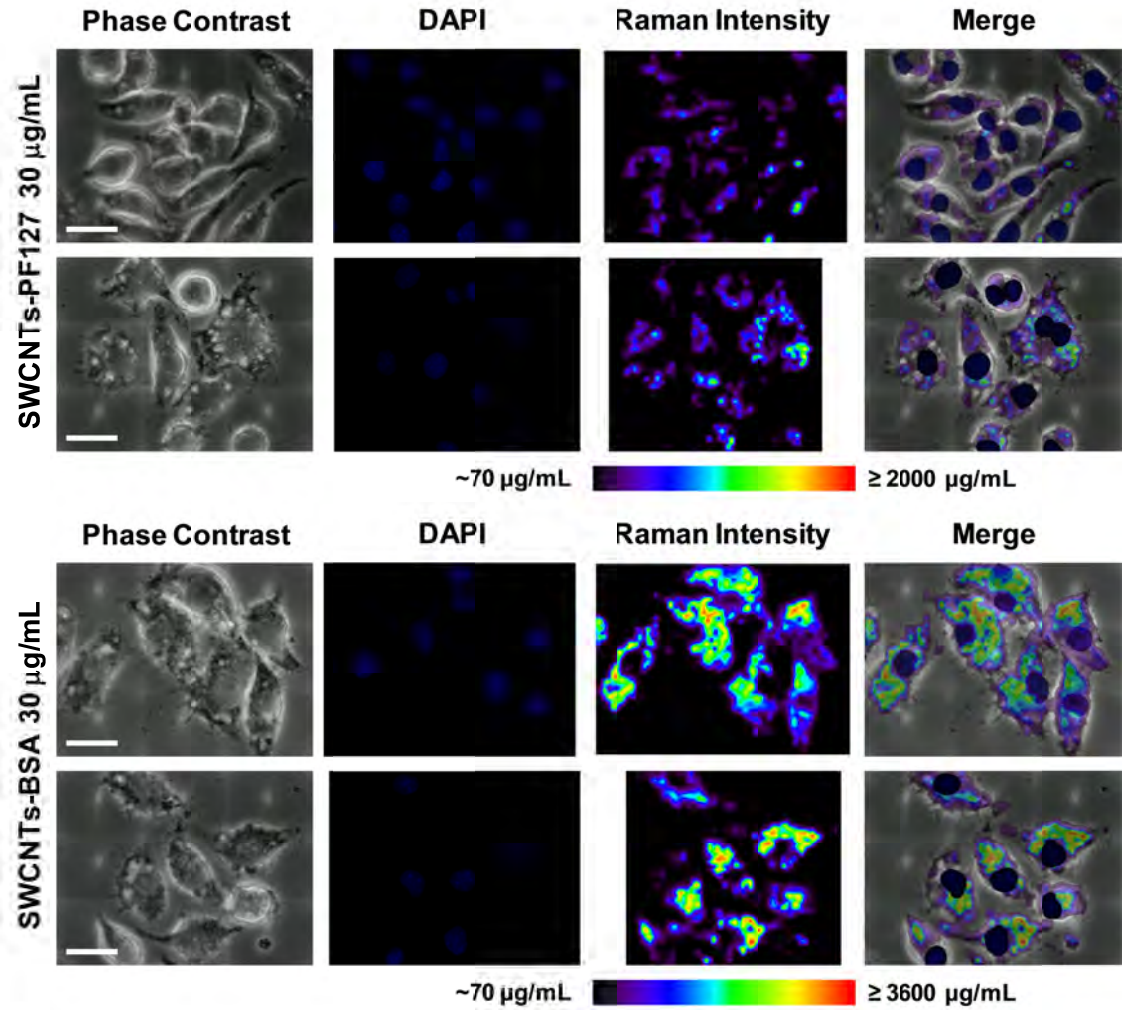

Figure S1. Raman intensity (heatmap) is localized peripheral to the nucleus. The nucleus is labeled by a DNA stain (DAPI). Co-registration of the phase image, nuclear image and Raman image show perinuclear localization of SWCNTs within the cell for both SWCNT-PF127 and SWCNTs-BSA. Scale bar represents 20 µm.

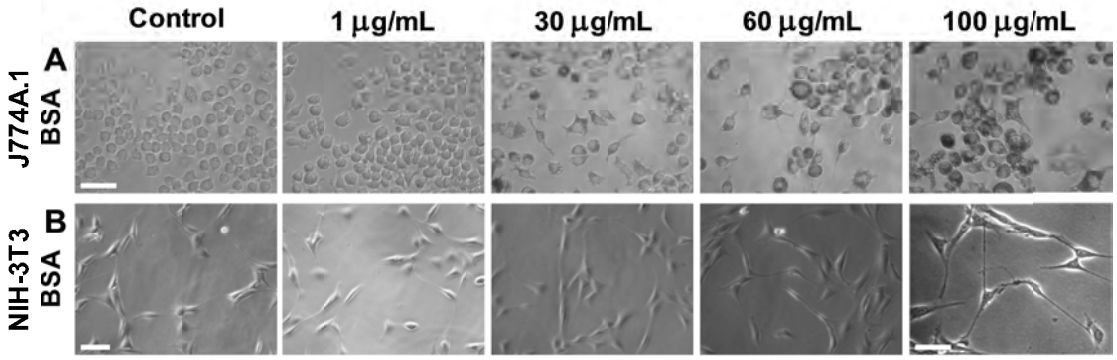

Figure S2. SWCNTs–BSA concentration-dependent effects on macrophage and fibroblast morphology. (A) Low magnification images show a dose-dependent change in morphology with noticeable phase dense regions for J774A.1 macrophages treated with SWCNTs–BSA. Scale bar represents 50 μm. (B) Low magnification images show no dramatic change in morphology for NIH-3T3 fibroblasts treated with increasing concentrations of SWCNTs–BSA. Scale bar represents 100 μm.

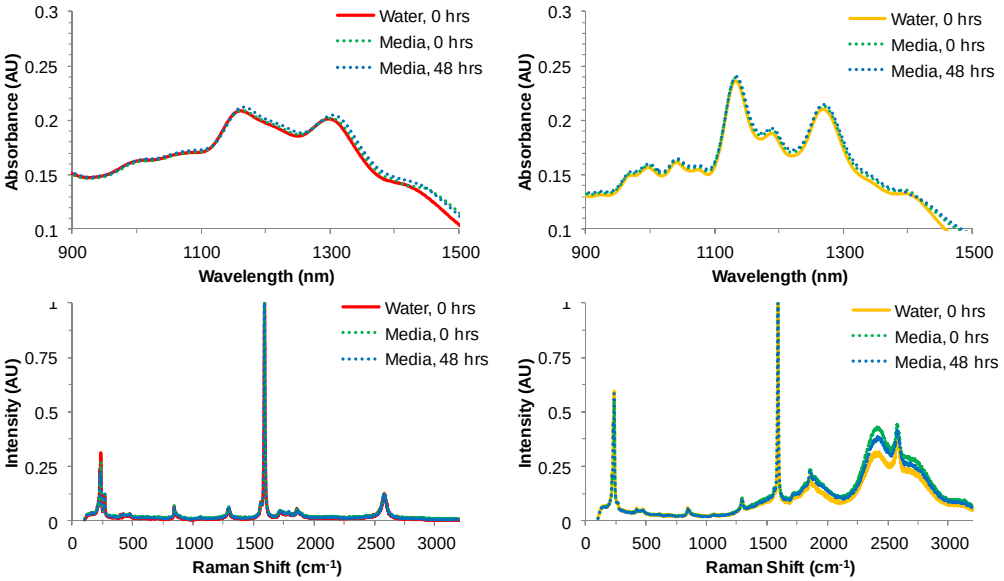

Figure S3. Spectroscopic analysis of SWCNT stability in complete cell culture media over 48 hrs. (A) NIR absorbance of SWCNTs-PF127 and SWCNTs-BSA as prepared in water (solid line) and in complete cell culture media at 0 and 48 hrs (broken lines). Absorbance spectra show that distinct van Hove peaks were maintained after 48 hrs in cell culture media. (B) Raman spectra of SWCNTs-PF127 and SWCNTs-BSA as prepared in water (solid line) and in complete cell culture media at 0 and 48 hrs (broken lines), normalized to the intensity of the G-band (at 1590 cm^{-1}). Raman spectra show no change in the D-band (at 1350 cm^{-1}) or RBM above 250 cm^{-1} after 48 hrs in cell culture media.