## Supporting Information

## Enabling sensitive phenotypic profiling of cancer-derived small extracellular vesicles using surface-enhanced Raman spectroscopy nanotags

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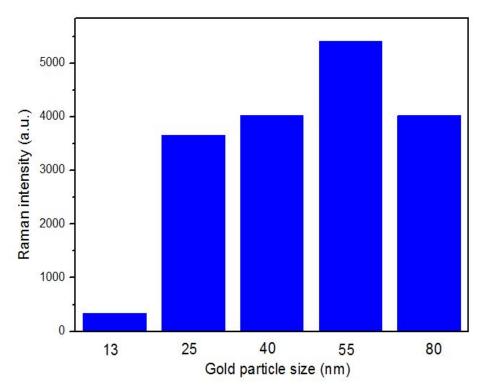


Figure S1. Raman intensity of DTNB on AuNPs at different sizes.

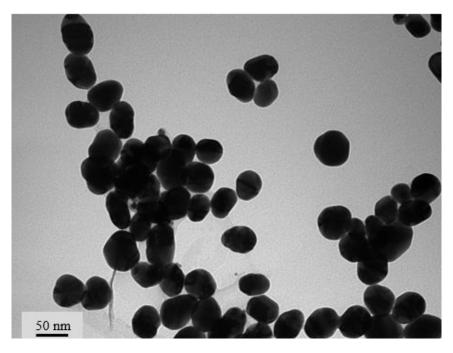


Figure S2. TEM image of AuNPs-DTNB-MIL-38 antibody (SERS nanotags).

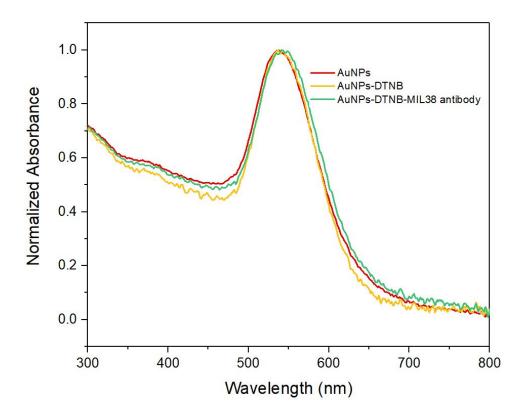


Figure S3. UV-vis absorption spectra of AuNPs, AuNPs-DTNB and AuNPs-DTNB-MIL-38 antibody (SERS nanotags).

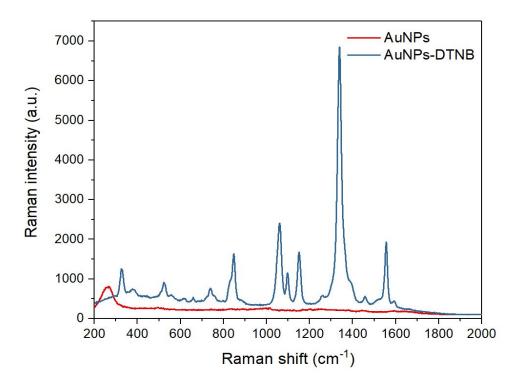


Figure S4. Raman spectra of AuNPs and AuNPs-DTNB.

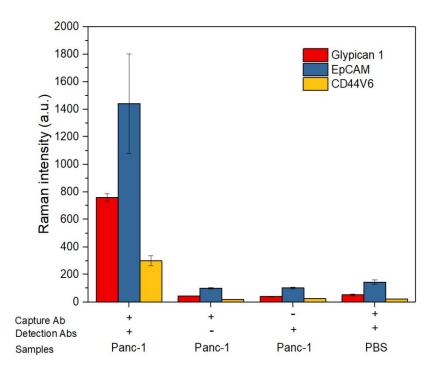


Figure S5. Specificity study of individual SERS nanotag for EV phenotypic profiling by using SERS assay (n=3).

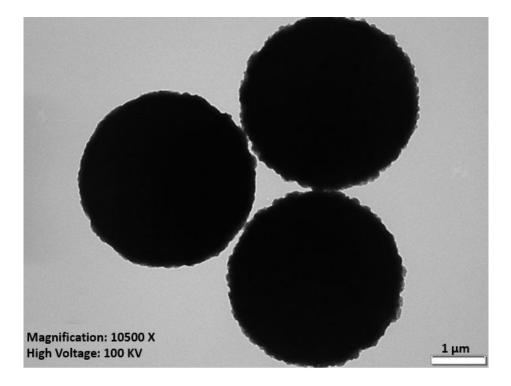


Figure S6.TEM image of the sandwich complex formed on magnetic beads, with conditioned EV concentration of  $1.2 \times 10^8$  particles/mL.

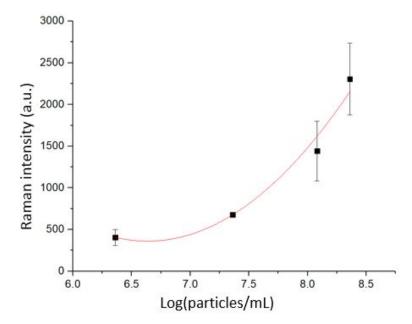


Figure S7. Correlation curve of EV concentration (Log (particles/mL)) and Raman intensity.

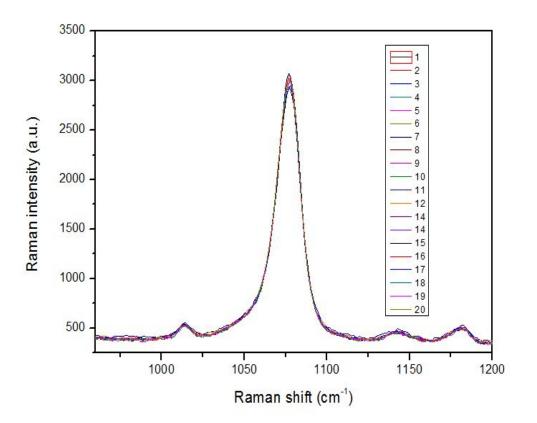


Figure S8. SERS spectra of the immunoassay with small EVs for 20 measurements.

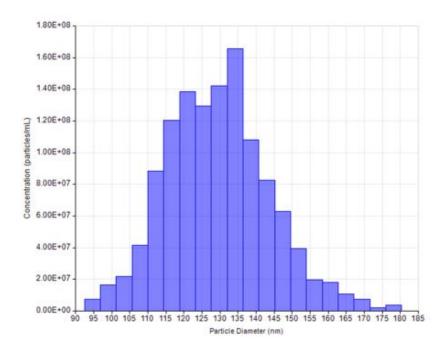


Figure S9. Size distribution and concentration of conditioned C3 EVs (1.2×10<sup>9</sup> particles/mL), measured by qNano.

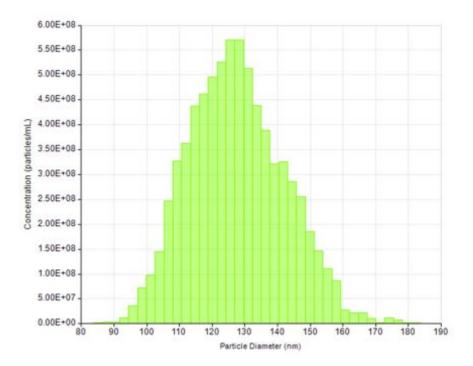


Figure S10. Size distribution and concentration of conditioned SW480 EVs (7.5×10<sup>9</sup> particles/mL), measured by qNano.