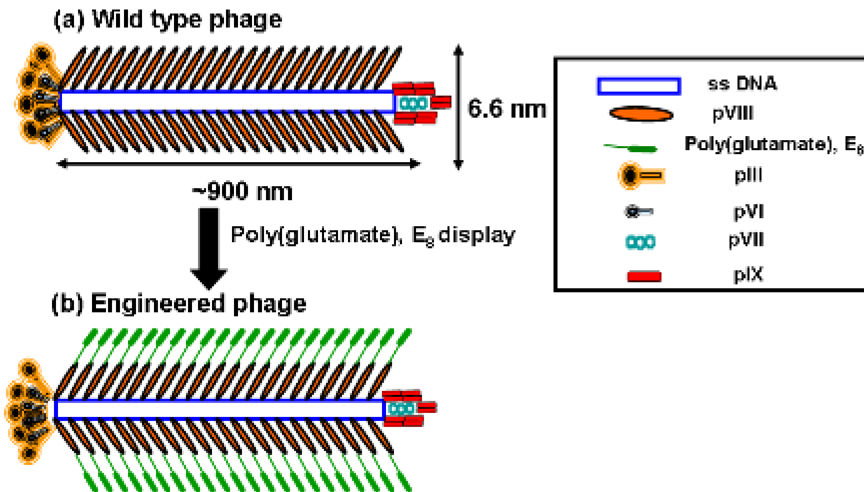

Scheme S1. Schematic illustration of displaying foreign peptide on the side wall of M13 phage through genetic engineering (not scaled). The foreign peptide is genetically fused to the N-terminus of pVIII (also called gP8) constituting the side wall of the M13 phage. The structure of M13 phage is a rod composed of ~2700 highly ordered copies of pVIII surrounding a circular single-stranded DNA. The DNA encodes 10 proteins including pVIII on the major coat (i.e., side wall) and four other structural proteins at two tips (called minor coats) such as pIII (5 copies) and pIX (5 copies). By inserting DNA encoding peptides into the genes of the coat proteins, the peptides are themselves displayed on the outer surface of the phage at the tips (e.g., pIII display at one tip and pIX display at another tip) and/or along the length (**pVIII display on the side wall**). **This is the principle of site-specifically displaying a foreign peptide on phage**. By *in vitro* or *in vivo* phage display technique, **a peptide that can specifically recognize a tumor cell or tissue can be identified and displayed at the tip (pIII, i.e., gP3) of the phage**(1-5). Different peptides can be simultaneously displayed at the tip and side wall of phage (e.g., the tumor-homing peptide on the tip and the liposome-interacting peptide on the side wall).

References:

1. De J, Chang YC, Samli KN, et al. Isolation of a Mycoplasma-specific binding peptide from an unbiased phage-displayed peptide library. Molecular Biosystems 2005; 1:149-57.
2. Hoffman JA, Laakkonen P, Porkka K, Bernasconi M, Ruoslahti E. In vivo and ex vivo selections using phage-displayed libraries. Phage: Display: A Practical Approach 2004:171-92.
3. Kolonin MG, Sun J, Do KA, et al. Synchronous selection of homing peptides for multiple tissues by in vivo phage display. Faseb Journal 2006; 20:979-+.
4. Pasqualini R, Ruoslahti E. Organ targeting in vivo using phage display peptide libraries. Nature 1996; 380:364-6.
5. Shukla GS, Krag DN. Phage display selection for cell-specific ligands: Development of a screening procedure suitable for small tumor specimens. Journal of Drug Targeting 2005; 13:7-18.

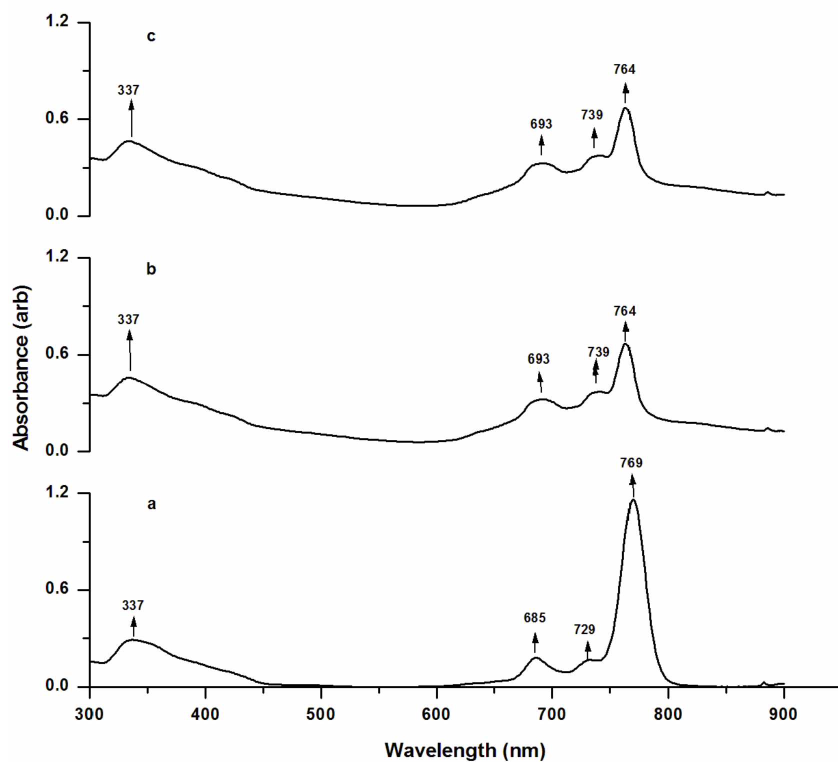

Figure S1. UV-Vis spectra of a) 10 μM ZnNC in DMSO, b) in liposome and c) in phage-liposome complex. The Q bands (600 – 800 nm) and Soret bands are indicated by arrows.

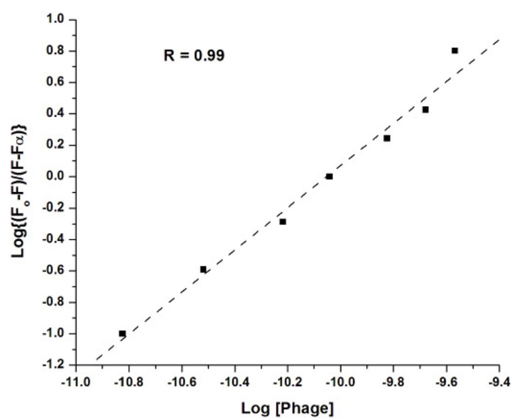

Figure S2. The double-logarithm plot obtained from experimental fluorescence spectral data, when the fluorescence intensity of ZnNC was measured as a function of increasing phage concentration. Slope of the linear plot is the number equivalent binding capacity (n), whereas the value of log[phage] at $\log[(F_o\text{-}F)/(F\text{-}F_\infty)] = 0$ equals the logarithm of the dissociation constant (K_{diss}). The reciprocal of K_{diss} is the binding constant K_b.

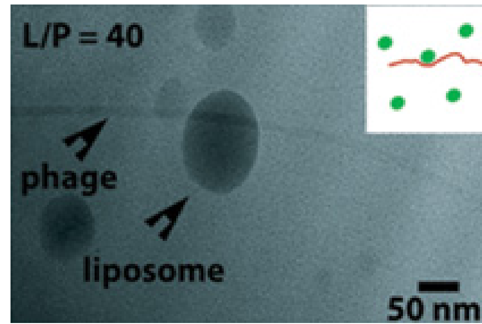

Figure S3. TEM images of the phage-liposome complexes at L/P = 40. The image was obtained by negatively staining the phage-liposome complexes using a mixture of 5% phosphotungstic acid and 2.5% trehalose (pH 7.3), 30 minutes after the complexation of liposomes and phage.

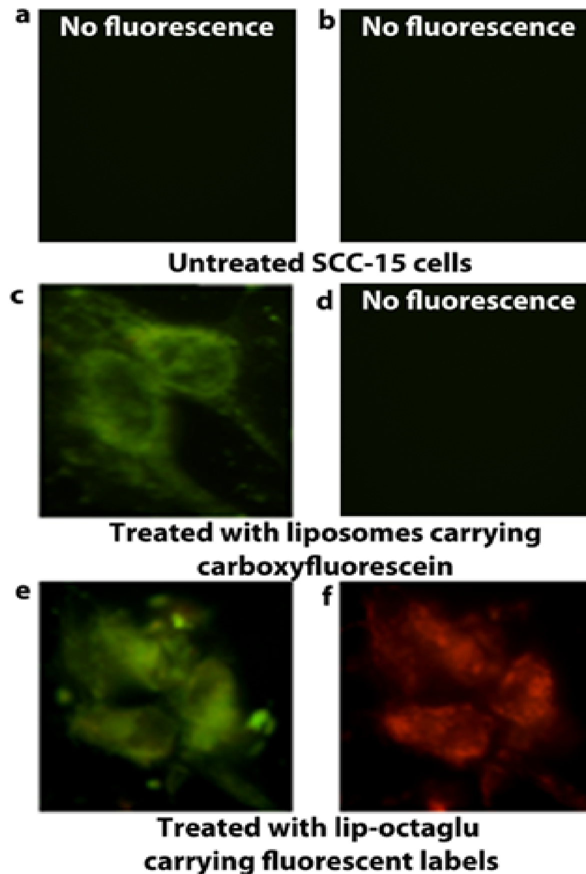

Figure S4. Fluorescence microscopic images of treated and untreated SCC-15 cells. (a) Of untreated cells under blue filter, where no fluorescence is observed. (b) Of Untreated cells under green filter, where no fluorescence is observed. (c) Cells treated with liposomes under the blue filter, where green fluorescence arises from carboxyfluorescein tag. (d) Cells observed under green filter, treated with liposomes, where no fluorescence is observed due to absence of phage. (e) Cells observed under blue filter where green fluorescence arises from carboxyfluorescein tagged nanowebs (i.e., lip-octaglu). (f) Cells observed under green filter where red fluorescence arises from the rhodamine-B tagged phages present in lip-octaglu. That both green and red fluorescence arises from same areas within the cells indicate that liposomes are bound to the phages.

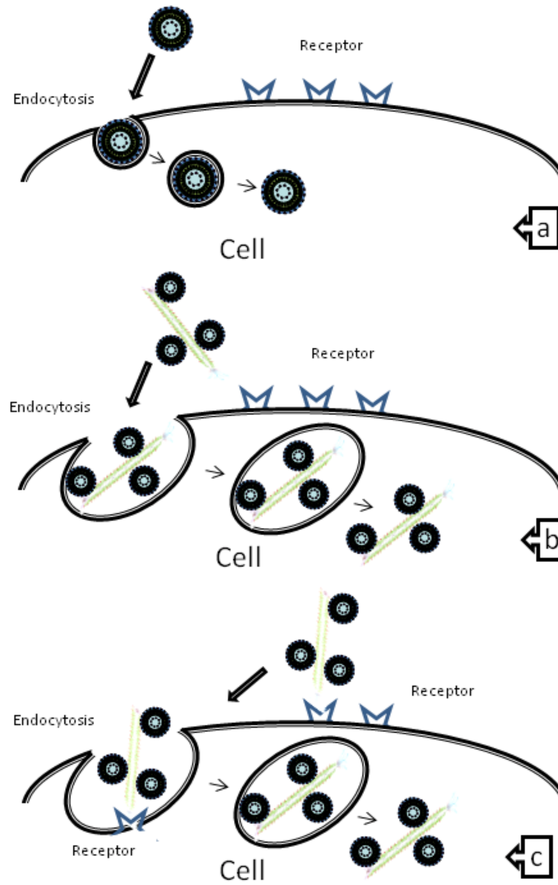

Figure S5. Proposed mechanism for the internalization of liposomes into cancer cell lines. In the absence of the phage (a) individual liposomes are engulfed into the cells through endocytosis, following which they are released inside the cells and the DOPE brings about a release of the drug by way of a pH triggered fusion of the bilayers. In the presence of the phage (b), the lamellar structure of phage-liposome complex permits the phage to bind more than one liposome per phage, endocytosis still occurs via liposome, however more amount of liposome is engulfed owing to the liposomes being attached to the phage. The glutamic acid in the phage can bring about fusion of adjacent liposomes at acidic pH conditions found inside cells and DOPE can trigger release of ZnNC through bilayer fusion. If the pIII (i.e., the tip) of the phage. (c) is engineered to carry target molecules having binding capabilities to over expressed receptors in cancer cells, then receptor mediated binding and endocytosis is expected, offering selective targeting capabilities to the complex. Figure drawn not to scale.