Supplementary file 1

Allosteric ligand-driven smart nanoconjugates for mutation-selective EGFR targeting: A precision approach to overcoming tyrosine kinase inhibitor resistance

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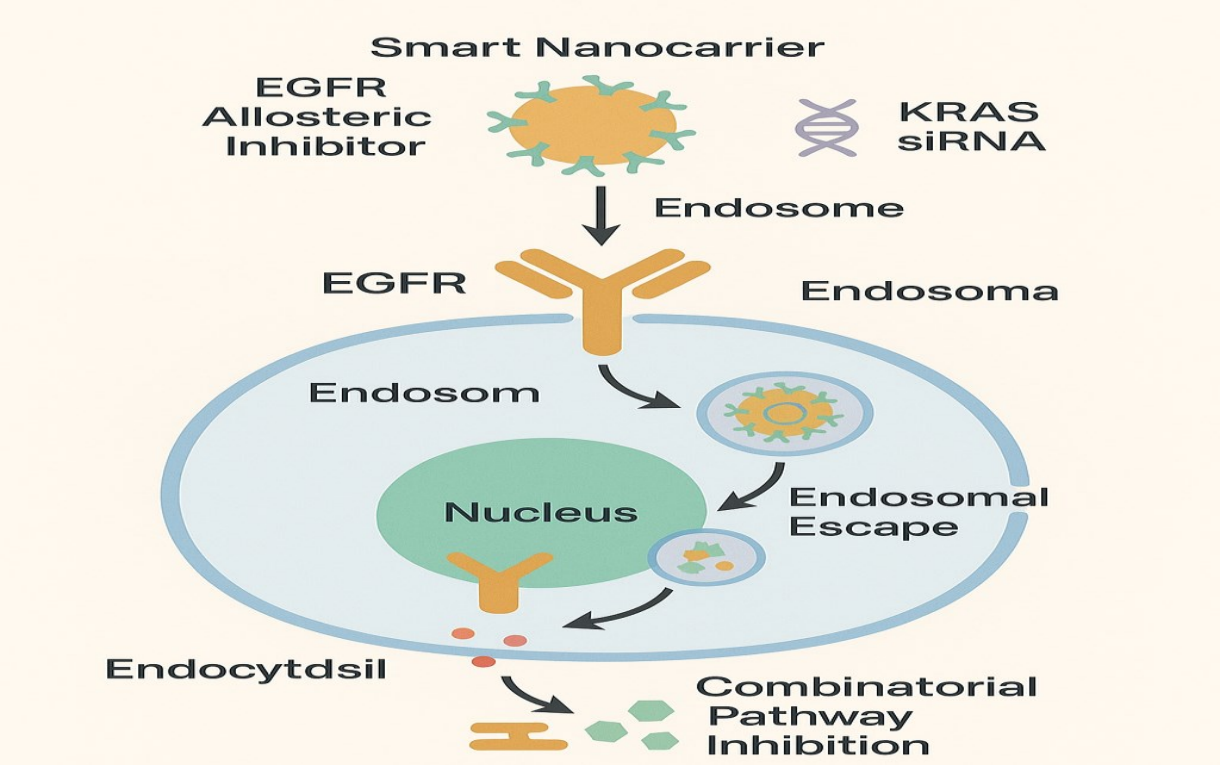

Figure S1: *Dual-functional nanoconjugate delivering both an allosteric EGFR inhibitor and siRNA targeting KRAS. Workflow includes targeted*

uptake, combinatorial pathway inhibition, and tumor regression. (Adapted from literature under Creative Commons license and redrawn by authors.)

Table S1: Strategies for Allosteric Ligand Conjugation to Nanocarriers

Conjugation Method	Chemistry Type	Compatible Ligands	Nanocarrier Compatibility	Reaction Conditions	Stability of Linkage	Common Applications
EDC/NHS Coupling	Amide bond formation	Carboxyl, amine-bearing	Liposomes, PLGA NPs, micelles	Mild aqueous (pH 5.5–7.5)	High (covalent)	Peptides, small-molecule ligands
Click Chemistry (CuAAC)	Azide–alkyne cycloaddition	Azide/alkyne-functional groups	Dendrimers, polymeric micelles, lipids	Requires Cu(I) catalyst, pH 7–8	Very High (bioorthogonal)	Small molecules, aptamers, fluorescent probes
Thiol–Maleimide Coupling	Michael addition	Thiol-containing ligands	PEGylated liposomes, nanogels	Mild, aqueous or organic media	High (stable thioether)	Allosteric inhibitors, antibodies
Schiff Base Formation	Aldehyde–amine	Amine or aldehyde-containing	Chitosan, dextran-based carriers	Aqueous, reversible at low pH	Moderate (reversible)	pH-sensitive release systems
PEGylation with Functional Ends	Pre-activated PEG derivatives	Any ligand with reactive group	Liposomes, polymers, dendritic systems	Room temp, aqueous/organic	High	Stealth delivery + targeting ligand attachment
Silane Coupling	Siloxane linkage	Hydroxyl, amine	Mesoporous silica NPs	Organic solvents or aqueous pH 4–5	High	Covalent immobilization of bioactives