Next Generation Cancer Therapeutics: Peptide Binder Impairing Oncogenic KRAS Signalling by Inhibition of KRAS–PDEd Interaction

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This project designs anti-cancer peptides that inhibit PDEd, a chaperone regulating KRAS signaling. Using the PDEd crystal structure (PDB: 4JV6), RFdiffusion generated peptide backbones, ProteinMPNN selected sequences predicted to fold correctly, and DynamicBind estimated binding affinities. Three peptide binders (PB1–PB3) were synthesized and tested in A549 lung cancer cells: after 48 hours at 400 μM, PB1, PB2, and PB3 reduced viability by ~80%, ~60%, and ~30%, respectively. To improve potency and reduce dosage, three strategies were implemented. (1) A polyarginine cell-penetrating peptide (CPP) with a linker was fused to PB1, yielding FPB1-CPP, which achieved ~80% inhibition at 50 μM. FPB1-CPP showed limited effects on non-cancerous BEAS-2B cells and enabled cisplatin dose reduction while maintaining IC50-level inhibition, suggesting potential to lessen combination-therapy side effects. (2) DNA-encoded delivery via a mammalian expression plasmid (pcDNA3.0-FPB1-CPP) produced intracellular FPB1-CPP; transfection of A549 cells with 2 μg plasmid (PEI) reduced viability by 40% versus empty vector, indicating a modality that may mitigate systemic toxicity. (3) To enhance PB3 uptake and lower synthesis cost, palmitic acid was conjugated to its N-terminus; the palmitoylated PB3 reduced A549 viability by 40% at 200 μM, a 30% improvement over unmodified PB3.Because tumor microenvironment influences resistance, efficacy was assessed in 3D multicellular tumor spheroids, where FPB1-CPP reduced viability by ~20% after two days. Tests confirmed FPB1-CPP works by blocking the KRAS pathway, reducing a key growth signal (Cyclin D1) to slow cancer cells.

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