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Targeted Modulation of SNAP23 for Treatment of RAS-Driven Cancers via Engineered Proteases, Heterobifunctional Small Molecules (PROTACs and RIPTACs), and Antibody-Conjugated Delivery

KRAS mutations drive roughly a quarter of all human cancers, yet approved KRAS inhibitors deliver only short-lived responses before resistance emerges, and combination strategies have been limited by severe toxicity. This invention targets SNAP23, a vesicular trafficking protein required by mutant KRAS to reach the cell surface to activate cancer-promoting signaling in addition to multiple survival pathways KRAS-driven cells require for survival. Preclinical ablation of the target results in ~80% tumor regression with selective toxicity in KRAS mutant cells. The invention encompasses targeted protein degraders designed to disrupt SNAP23 function, offering a durable, combinable treatment paradigm for pancreatic, colorectal, and lung cancers where no adequate long-term therapy currently exists.

Applications

- The primary commercial application is a therapeutic for KRAS-driven solid tumors, with anchor indications in pancreatic ductal adenocarcinoma, colorectal adenocarcinoma, and non-small-cell lung adenocarcinoma. Conservative US-only addressable populations range from approximately 30,000 to 90,000 patients per year depending on biomarker stratification, with substantially larger ex-US populations. The unmet need is acute: median overall survival in metastatic PDAC remains under 12 months despite all available therapy, and no

allele-agnostic KRAS-directed agent has achieved durable disease control in this setting.

- Likely customers include patients with KRAS-mutant cancers across all oncogenic alleles (since the SNAP23 dependency is allele-agnostic), oncologists and academic medical centers, and pharmaceutical developers seeking differentiated KRAS-targeted assets and resistance-orthogonal combination partners for the anti–PD-1 immunotherapy backbone. The DAC-format embodiment is particularly well positioned for checkpoint combination given that ADC-class delivery has already demonstrated FDA-validated combinability with pembrolizumab (EV-302 in urothelial carcinoma; DESTINY-Lung06).
- The RIPTAC embodiment additionally opens application to KRAS-mutant tumors carrying CRBN, VHL, or proteasome-pathway alterations that confer resistance to PROTAC-class agents, a clinically emerging resistance mode for which no current modality offers a clean answer.
- Secondary applications include research reagents - engineered SNAP23-cleaving proteases, SNAP23 PROTAC tool compounds, and SNAP23 RIPTAC chemical biology probes, for the academic community studying RAS trafficking, SNARE biology, induced-proximity pharmacology, and small non-coding RNA regulation of GTPases.

Advantages

- Existing KRAS-directed approaches each have material limitations:
- Direct allele-specific KRAS inhibitors and PROTACs (sotorasib/Lumakras, adagrasib/Krazati, setidegrasib/ASP3082, VS-7375, ARV-806) provide single-allele coverage and produce polyclonal acquired resistance within months. Combination with second systemic agents to close escape routes has been blocked by overlapping toxicity. Pan-RAS(ON) inhibitors (RMC-6236/daraxonrasib) improve efficacy in PDAC (mOS 13.2 vs. 6.7 months, HR 0.40) but at the cost of systemic toxicity (38% Gr≥3 TRAE; 91% rash) that constrains chronic dosing and IO combination. Upstream RTK inhibitors (cetuximab, panitumumab) have minimal single-agent activity in KRAS-mutant disease.
- SNAP23-directed therapy provides several mechanistically distinct advantages:
- It is KRAS-selective: SNAP23 dependence is specific to KRAS trafficking, with HRAS and NRAS subcellular localization unaffected, narrowing on-target activity to the relevant oncogene. It is allele-agnostic: because SNAP23 acts on KRAS

trafficking rather than the active site, the dependency holds across all oncogenic KRAS alleles (G12C, G12D, G12V, G13D, Q61, amplification), providing coverage where allele-specific agents fail. It is resistance-orthogonal: the trafficking node is not subject to the KRAS active-site secondary mutations (Y96D/C, H95, R68S) that drive escape from G12C and G12D inhibitors. It is genetically validated in vivo: ~80% tumor regression in KRAS-mutant DLD-1 xenografts with SNARE knockout, no effect in isogenic KRAS-wild-type controls, plus a significant survival association ($p = 0.0003$) in TCGA pancreatic adenocarcinoma. It is tractable for tumor-selective delivery: SNAP23 is broadly expressed, but DAC-format delivery to a tumor-restricted antigen confines exposure to cancer cells, directly addressing the on-target/off-tissue toxicity that has defeated systemic combination approaches. And it is compatible with combination architecture: as a payload mechanistically distinct from KRAS itself, a SNAP23-directed agent can be co-formulated as the second arm of a dual-payload DAC together with a KRAS PROTAC, enabling combinatorial mechanism without combinatorial toxicity.

- The PROTAC and RIPTAC embodiments offer complementary advantages within this framework. PROTACs degrade SNAP23 catalytically, recapitulating the genetic-knockout phenotype most directly and providing the strongest mechanistic match to the published in vivo regression data. RIPTACs, by contrast, do not deplete SNAP23 and therefore do not depend on E3 ligase competence, proteasome function, or cellular degradation capacity. a meaningful advantage given the documented emergence of CRBN- and proteasome-mediated resistance to clinical PROTACs. RIPTACs additionally exploit SNAP23 as a co-presence selectivity filter rather than as the directly drugged effector, potentially achieving tumor selectivity through a route that does not require the trafficking pathway itself to be the lethal lesion.

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