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PERSPECTIVE

Pan-KRAS inhibition: unlocking broad-spectrum targeted therapy for *KRAS*-mutant cancers

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KRAS is a critical proto-oncogene and molecular switch that is frequently mutated in human cancers. Oncogenic mutations, primarily at codons 12, 13, and 61, lock KRAS into a GTP-bound active state, thus resulting in constitutive signaling through downstream effectors such as RAF and phosphoinositide 3-kinase (PI3K)[1]. These alterations are highly prevalent in pancreatic cancer, colorectal cancer (CRC), and non-small cell lung cancer (NSCLC), and they drive tumor initiation, progression, and therapy resistance.

The discovery of cystine-specific targeting of the $KRAS^{G12C}$ mutation was a groundbreaking oncology milestone[2]. This advance culminated in the development and regulatory approval of allele-specific inhibitors such as sotorasib[3,4] and adagrasib[5,6], which covalently bind the mutant cysteine residue and stabilize KRAS in its inactive GDP-bound conformation. These agents achieve clinically meaningful responses in patients with $KRAS^{G12C}$-mutant NSCLC and other malignancies; therefore, direct KRAS inhibition is a viable therapeutic strategy.

However, the clinical efficacy of G12C-specific inhibitors is often limited by intrinsic and acquired resistance mechanisms[7]. Moreover, patients with numerous clinically relevant KRAS variants, including G12D, G12V, and G13D, remain underserved by mutation-specific approaches[8]. The structural and biochemical heterogeneity among these mutants complicates the development of broad-spectrum inhibitors, whereas adaptive feedback signaling and pathway reactivation further constrain durable responses. Herein, we describe the therapeutic promise of pan-KRAS inhibition by synthesizing insights from our prior investigations and clinical observations, including systematic analyses of the evolutionary trajectory of pan-KRAS inhibitors, comprehensive evaluation of the current clinical landscape, and emerging mechanistic insights. This innovative therapeutic strategy is designed to concurrently target multiple oncogenic KRAS variants, thereby addressing a long-standing challenge in *KRAS*-driven malignancies. By systematically reviewing ongoing clinical trials and emphasizing the development of next-generation KRAS-targeted agents, we aim to provide a comprehensive and forward-looking appraisal of this rapidly advancing field. Collectively, these perspectives highlight the potential for a paradigm shift in the therapeutic management of *KRAS*-mutant cancers.

Pan-KRAS inhibitors: broad-spectrum targeting beyond allele-specific therapies

After the successful development of inhibitors targeting $KRAS^{G12C}$, research efforts expanded to address other clinically significant KRAS mutations, notably $KRAS^{G12D}$, which is highly prevalent in colorectal and pancreatic carcinomas. Mirati Therapeutics made a critical contribution with the development of MRTX1133[9], a selective $KRAS^{G12D}$ inhibitor that showed initial promise but encountered limitations in clinical advancement, because of its unfavorable pharmacokinetic profile. Nevertheless, therapeutic targeting of KRAS remains highly challenging because of the diversity and complexity of its mutations. A considerable number of tumors bear less common KRAS variants, such as G12R, G12A, and Q61H, or exhibit KRAS wild-type amplification, for which effective targeted therapies remain lacking. The development of allele-specific inhibitors to achieve broad coverage

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across *KRAS*-driven cancers remains a formidable and time-consuming endeavor in precision oncology.

The field of KRAS targeting markedly evolved with the emergence of pan-KRAS inhibitors, which concurrently inhibit multiple KRAS mutations. A notable example is BI-2865[10], developed by Boehringer Ingelheim, which demonstrates potent activity against a range of KRAS mutations, including G12C and G12D. Derived from the earlier G12C-selective inhibitor BI-0474[11], BI-2865 was developed by removal of the acrylamide piperazine moiety, which is responsible for covalent binding to cysteine 12 and subsequent structural optimization. BI-2865 exhibits consistent inhibitory potency across Ba/F3 cell lines carrying diverse KRAS mutations, with an IC_{50} of approximately 140 nM. Binding affinity assays have revealed that BI-2865 selectively binds the GDP-bound state of KRAS, and displays high affinity (K_D = 4.5–32 nM) toward both wild-type and various mutant KRAS proteins, while maintaining selectivity against NRAS and HRAS. At the cellular level, it has been found to effectively suppress phosphorylation of ERK and AKT in *KRAS*-mutant models. Although BI-2865 inhibits wild-type KRAS in biochemical assays, it shows no significant toxicity in normal cells with low KRAS dependency, and it does not substantially affect ERK or AKT signaling in these cells, thereby suggesting a favorable therapeutic window centered on *KRAS*-driven malignancies. Further optimization yielded BI-2493[12], a spirocyclic derivative with improved pharmacokinetics suitable for oral administration. This compound has been observed to significantly inhibit tumor growth in multiple xenograft models bearing different KRAS mutations, without toxicity. Subsequent development of BI-3706674, which is now in clinical trials, has built upon this progress.

The suboptimal efficacy of $KRAS^{G12C}$-GDP selective inhibitors in clinical settings stems from adaptive resistance mechanisms that enhance the drug-insensitive KRAS-GTP (on) state. In contrast, dual-state inhibitors overcome this limitation by simultaneously targeting both KRAS conformations and directly suppressing the expanding active KRAS pool under therapeutic pressure. This approach effectively counters key resistance drivers, such as KRAS amplification and RTK-mediated KRAS (on) accumulation, thus enabling sustained target suppression, prolonged efficacy under growth factor challenge, and tumor regression in resistant settings, as demonstrated by agents such as BBO-8520[13]. Consequently, interest is growing in developing inhibitors that target both the inactive (off) and active (on) states of KRAS to achieve more durable clinical responses. Building on the optimized $KRAS^{G12D}$ inhibitor compound 31[14], we have conducted systematic structural modifications by removing the cyclobutane-substituted dimethylamino group to decrease interaction with Asp12, and by introducing a series of polar and nonpolar substituents to strengthen engagement with conserved residues in the P-loop region. These efforts yielded MCB-294[15], a potent and selective pan-KRAS inhibitor capable of binding both the inactive (GDP-bound; off) and active (GTP-bound; on) states of KRAS. Co-crystal structural analyses demonstrated that the (*R*)-3-methyl-3-hydroxypiperidine moiety of MCB-294 establishes critical interactions within the switch II pocket through a direct hydrogen bond with tyrosine 96 and a water-mediated hydrogen-bond network with glycine 10 and threonine 58. Although MCB-294 and BI-2865 both occupy the switch II allosteric site, MCB-294 notably extends into the P-loop region *via* this hydrogen-bond network, thereby addressing a previously unoccupied cavity and enabling dual-state inhibition. In functional assays, MCB-294 exhibited potent growth inhibition across multiple *KRAS*-driven tumor cell lines, while showing minimal activity (IC_{50} > 1,000 nM) in models driven by *NRAS*, *EGFR*, or *BRAF* mutations, as well as in normal cell lines. Moreover, in both cell line–derived and patient-derived xenograft models bearing KRAS mutations, MCB-294 significantly suppressed tumor growth without inducing observable toxicity, as evidenced by stable body weights. These results position MCB-294 as a promising broad-spectrum inhibitor with compelling *in vitro* and *in vivo* activity against diverse KRAS mutations. This agent might offer a potential therapeutic strategy that surpasses the limitations of GDP-state-selective KRAS inhibition. MCB-294 has been found to effectively overcome $KRAS^{G12C}$ inhibitor resistance and to enhance tumor immune cell infiltration, thus suggesting potential synergy with anti-PD-1 therapy. Strikingly, it has demonstrated superior anti-tumor efficacy as both a monotherapy and in combination with anti-EGFR therapy.

AMG 410 is another recently developed dual-state KRAS inhibitor designed to simultaneously target both the GTP-bound and GDP-bound conformations of KRAS[16]. In preclinical studies, AMG 410 has demonstrated potent antitumor efficacy, including tumor growth inhibition and regression, across multiple xenograft models of CRC, pancreatic cancer, and lung cancer carrying diverse KRAS mutations, such as G12D, G12V, G12C, and G13D. On the basis of these promising results, a clinical trial is evaluating AMG 410 in patients with advanced solid tumors. Dual inhibition of both KRAS states is an emerging therapeutic strategy in the development of pan-KRAS inhibitors. By circumventing the limitations of state-selective targeting, this approach might mitigate adaptive resistance mechanisms and achieve more durable clinical responses. AMG 410 exemplifies this advanced class of inhibitors and offers renewed hope for effective treatment of *KRAS*-driven malignancies.

Alongside these efforts, numerous other pan-KRAS inhibitors are advancing through clinical development (**Table 1**), thus underscoring the growing momentum toward broad-spectrum targeting of *KRAS*-driven cancers. Compounds such as BI-2865 and MCB-294 represent a strategic shift from

Table 1 Pan-KRAS targeting drugs currently in clinical trials

Drug	Sponsor	Disease setting	Clinical trial/phase
JAB-23E73	Jacobio Pharmaceuticals	Monotherapy (NSCLC, CRC, PDAC, and others)	NCT06973564 phase 1/2
AMG 410	Amgen	Monotherapy or combination with (NSCLC, CRC, PDAC, and others): Panitumumab (CRC and PDAC) Pembrolizumab (advanced or metastatic solid tumors with *KRAS* mutations)	NCT07094113 phase I
BGB-53038	BeiGene	Monotherapy or combination with (advanced or metastatic solid tumors with *KRAS* mutations or amplifications): Tislelizumab (NSCLC) Cetuximab (CRC)	NCT06585488 phase I
BI-3706674	Boehringer Ingelheim	Monotherapy (GAC, EAC, and GEJAC)	NCT06056024 phase I
PF-07934040	Pfizer	Monotherapy (NSCLC, CRC, and PDAC) or combination with: Gemcitabine + Nab-paclitaxel (PDAC) Cetuximab (CRC) FOLFOX + bevacizumab (CRC) Pembrolizumab (NSCLC) Pembrolizumab + platinum chemotherapy (NSCLC)	NCT06447662 phase I
LY-4066434	Eli Lilly and Company	Monotherapy or combination with (advanced or metastatic solid tumors with *KRAS* mutations): Cetuximab Nab-paclitaxel Gemcitabine Oxaliplatin Leucovorin Irinotecan 5-Fluorouracil Carboplatin Cisplatin Pemetrexed Pembrolizumab	NCT06607185 phase I
YL-17231	Shanghai YingLi Pharmaceutical Co., Ltd.	Monotherapy (advanced solid tumors bearing mutations in *KRAS*, *HRAS*, or *NRAS*)	NCT06096974 phase I

CRC, colorectal cancer; EAC, esophageal adenocarcinoma; GAC, gastric adenocarcinoma; GEJAC, gastroesophageal junction adenocarcinoma; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

mutation-specific inhibition toward a universal therapeutic strategy with potential to overcome the limitations of earlier allele-restricted agents. This approach is particularly promising for tumors bearing rare KRAS variants beyond G12C and G12D, by offering a more comprehensive treatment paradigm in precision oncology (**Figure 1**).

KRAS molecular glues: beyond conventional inhibitors toward tri-complex strategies

RMC-7977 is a first-in-class, orally bioavailable molecular glue that functions as a potent and selective pan-RAS (on) inhibitor[17]. Its mechanism of action involves initial high-affinity binding to the intracellular chaperone cyclophilin A (CypA) (**Figure 1**). The resulting RMC-7977–CypA complex then engages the active, GTP-bound form of diverse RAS mutants, by forming a stable ternary complex that sterically occludes effector interaction and abrogates downstream MAPK and PI3K signaling. Subsequently, activated RAS is prevented from engaging its effectors, and GTP hydrolysis is pharmacologically stimulated. The drug-bound CypA complexes modulate residues within the switch II motif of RAS, thereby coordinating nucleophilic attack on the γ-phosphate of GTP in a mutation-specific manner. Preclinical evaluations have demonstrated broad and potent antitumor efficacy across multiple *RAS*-driven malignancies including pancreatic cancer, NSCLC, and CRC, even in models resistant to $KRAS^{G12C}$-specific inhibitors. A clinically distinguishing feature is its tumor-selective lethality: RMC-7977 induces

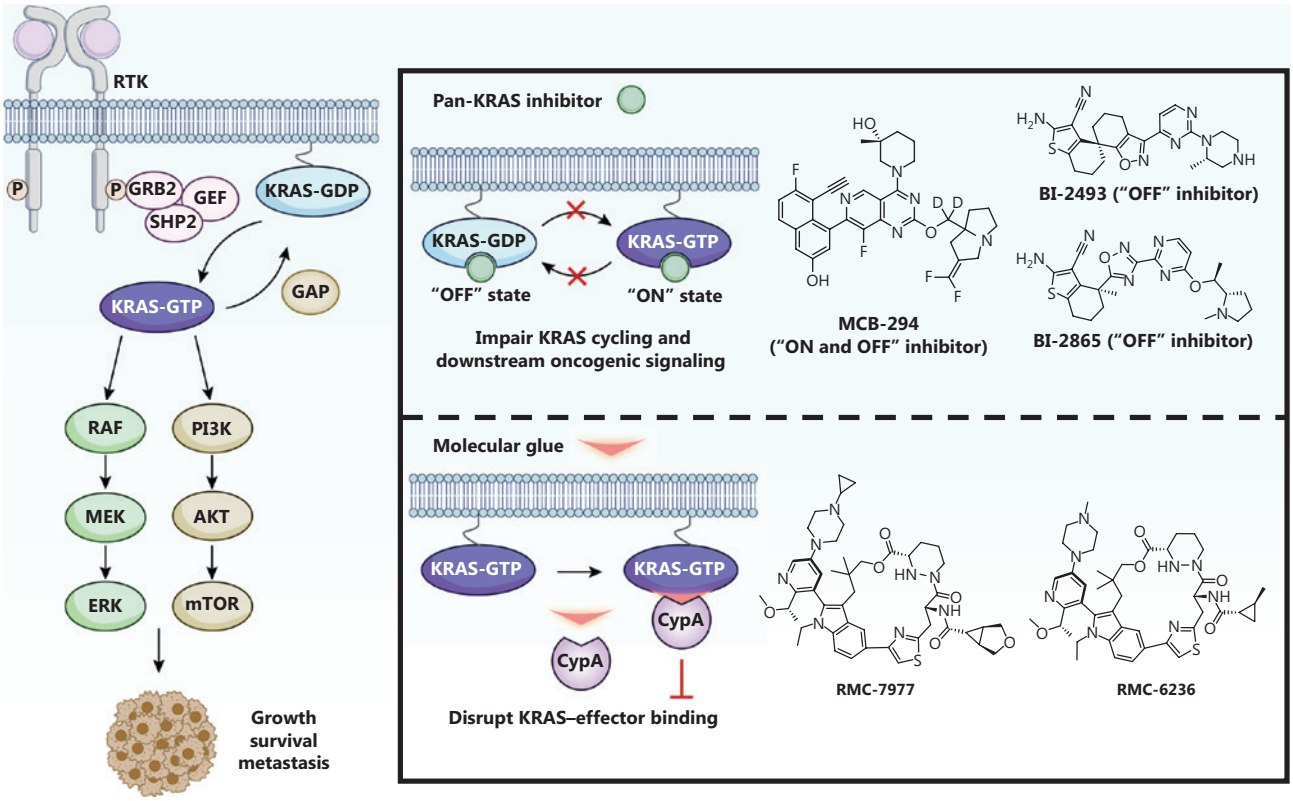


Figure 1 Targeting KRAS signaling pathways in cancer therapy: inhibition of KRAS activation and KRAS-effector interactions. The canonical KRAS signaling pathway (left). Mechanism of action of direct pan-KRAS inhibitors (right). Pan-KRAS off inhibitors (e.g., BI-2493 and BI-2865) function by binding and stabilizing the inactive, off-state (GDP-bound) form of KRAS. This stabilization impedes GTP loading and effectively prevents downstream pathway activation. MCB-294 is a dual inhibitor that engages both the off-state (GDP-bound) and on-state (GTP-bound) forms of KRAS, thus resulting in broader suppression of *KRAS*-driven signaling. KRAS molecular glues (e.g., RMC-7977 and RMC-6236) disrupt KRAS-effector interactions in a cyclophilin A (CypA)-dependent manner, thereby abrogating downstream oncogenic signaling.

apoptosis in transformed cells while eliciting only transient and reversible cytostatic effects in normal tissues, thus supporting a plausible therapeutic window. Furthermore, the YAP-TAZ pathway contributes to MYC-mediated resistance to RMC-7977. Therefore, dual targeting of both the RAS and YAP-TAZ-TEAD pathways might provide a promising therapeutic strategy for pancreatic ductal adenocarcinoma bearing such alterations[17].

As a foundational proof-of-concept agent, RMC-7977 indicated the therapeutic feasibility of pan-RAS inhibition *via* molecular glue–mediated suppression and directly enabled the development of its clinical successor, RMC-6236 (daraxonrasib)[18]. RMC-6236 retains the core molecular glue mechanism, by facilitating CypA-dependent ternary complex formation and broad-spectrum RAS pathway inhibition. In advanced-phase trials, it is currently showing compelling clinical activity, with particular promise in historically treatment-refractory *RAS*-mutant malignancies such as pancreatic adenocarcinoma and NSCLC.

Therapeutic KRAS degradation: navigating preclinical efficacy and clinical challenges for a new class of anticancer agents

The next frontier in oncogenic KRAS targeting is the development of protein degradation therapies. Unlike allele-specific inhibitors, pan-KRAS degraders are aimed at entirely eliminating KRAS protein, independently of mutational status, by exploiting the ubiquitin–proteasome system (**Figure 2**). This paradigm-shifting therapeutic strategy has potential applicability across a broad range of *KRAS*-driven malignancies.

ACBI3, developed by Boehringer Ingelheim, is among the first rationally designed pan-KRAS degraders demonstrating high potency and comprehensive allele coverage[19]. This heterobifunctional proteolysis-targeting chimera (PROTAC)

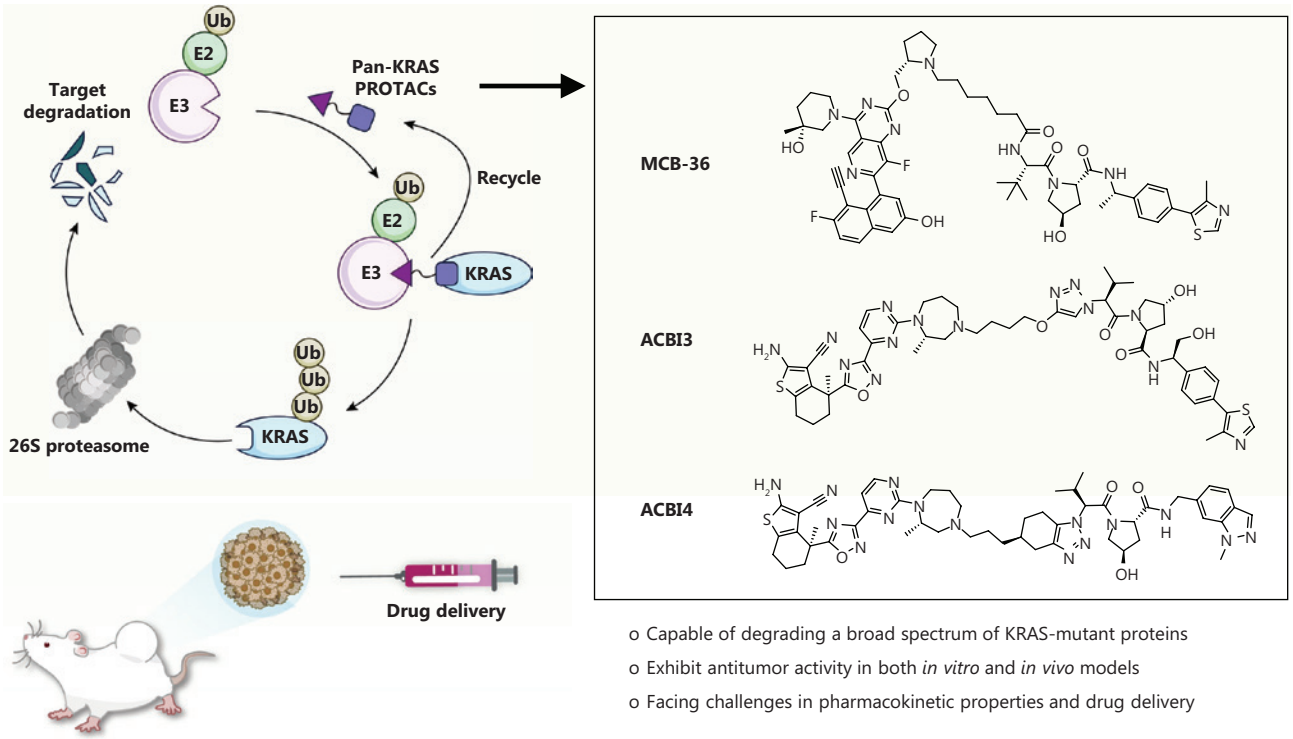


Figure 2 Targeted degradation of KRAS *via* PROTACs. Mechanism of action of pan-KRAS PROTACs (left). These molecules consist of a KRAS-binding ligand associated with an E3 ubiquitin ligase recruiter. After simultaneous binding to both KRAS and an E3 ubiquitin ligase, the formation of a ternary complex facilitates the polyubiquitination of KRAS. The ubiquitinated KRAS is subsequently recognized and degraded by the 26S proteasome, and the E3 ligase and the PROTAC molecule are recycled for subsequent rounds of degradation. Representative chemical structures of developed pan-KRAS PROTACs, including MCB-36, ACBI3, and ACBI4 (right), are shown. These molecules, designed to target a broad spectrum of KRAS mutants for degradation, offer a promising therapeutic strategy to overcome *KRAS*-driven oncogenesis. PROTACs, proteolysis-targeting chimeras.

comprises 3 critical elements: (1) a warhead that binds a conserved shallow pocket on KRAS, and engages both mutant variants (including G12D, G12V, and G13D) and wild-type protein; (2) a ligand that recruits the von Hippel-Lindau (VHL) or Cereblon E3 ubiquitin ligase complex; and (3) a linker that spatially optimizes the warhead-ligand interaction, thereby facilitating effective ubiquitination. Structural insights have revealed that ACBI3 stabilizes a ternary complex between KRAS and the VHL–Elongin B–Elongin C (VCB) complex. Key interactions include hydrogen bonding *via* water molecules at the triazole moiety, as well as direct hydrogen bonds between the hydroxymethyl group and His110 of VCB and Glu98 of KRAS. In preclinical models, ACBI3 induces robust and selective KRAS degradation, thereby resulting in sustained suppression of MAPK signaling and pronounced antiproliferative effects in *KRAS*-mutant cell lines. Notably, in GP2D xenograft models, ACBI3 administration (30 $mg \cdot kg^{-1}$) has been found to lead to significant tumor regression. Importantly, this treatment exhibits a favorable therapeutic window with minimal effects on wild-type *KRAS*-dependent tissues. As a peer-validated development candidate, ACBI3 not only provides a compelling proof of concept for pan-KRAS degradation but also establishes a structural and mechanistic foundation for future degrader therapeutics aimed at eradicating this once "undruggable" oncoprotein.

ACBI4, a next-generation pan-KRAS PROTAC degrader, was designed through structural optimization of predecessor ACBI3[20]. While retaining the core heterobifunctional architecture typical of PROTAC molecules, ACBI4 incorporates modifications in its E3 ligase ligand and linker chemistry that enhance its pharmacological profile. Whereas most KRAS inhibitors developed to date have been designed to bind the GDP-bound off state, ACBI4 was rationally engineered to engage and degrade the active, GTP-bound on state of KRAS. ACBI4 recruits the VHL E3 ubiquitin ligase and forms a highly cooperative and stable ternary complex with KRAS (on), thus enabling efficient ubiquitination and proteasomal degradation even with ligands of modest intrinsic affinity. As a pan-KRAS degrader, ACBI4 broadly targets oncogenic KRAS alleles. This compound potently degrades the therapeutically challenging

$KRAS^{G12R}$ mutation (DC_{50} = 151 nM; Dmax = 82%) and outperforms ACBI3 (DC_{50} = 961 nM; Dmax = 50%). Critically, ACBI4 also effectively targets KRAS Q61K in Calu-6 cells (DC_{50} = 157 nM; Dmax = 68%), whereas ACBI3 is inactive, thus demonstrating ACBI4's superior breadth and potency. In cell-based assays, ACBI4 induces rapid and profound degradation of KRAS mutants, and leads to robust suppression of downstream signaling pathways and marked antiproliferative effects. Beyond its immediate cellular effects on KRAS degradation, ACBI4 is also a valuable chemical probe for validating targeting the active state of KRAS with PROTACs, as a tractable therapeutic vulnerability. Although ACBI4 is still in early development stages, its emergence represents both a conceptual breakthrough and a practical advance in KRAS-targeted drug discovery that may open new avenues for therapeutic intervention in *KRAS*-driven malignancies in which conventional inhibitors have shown limited efficacy. Its development underscores a strategic focus on translating preclinical innovation into viable therapeutic candidates with broader clinical applicability.

MCB-36 is a mechanistically innovative and therapeutically promising agent within the emerging class of pan-KRAS degraders[15]. Developed through rational optimization of the pan-KRAS-targeting warhead MCB-294, MCB-36 is a bifunctional PROTAC molecule that recruits the VHL E3 ubiquitin ligase complex and subsequently induces potent and sustained degradation of KRAS across multiple mutant isoforms. A key advantage of MCB-36 is its prolonged activity. In direct comparisons, it has been found to sustain KRAS degradation and consequent MAPK pathway suppression (*via* reduced ERK phosphorylation) for more than 72 h, thereby outperforming its precursor. Because this compound exhibits robust anti-tumor activity, including potent activity against $KRAS^{G12C}$ inhibitor-resistant models, it has potential to address a critical unmet need in overcoming therapeutic resistance. Furthermore, MCB-36 induces favorable immunomodulatory changes within the tumor microenvironment and therefore might potentially be combined with immune-based therapies. As an extensively profiled chemical probe, MCB-36 provides fundamental insights into the biological consequences of pan-KRAS loss and has established a strong mechanistic rationale for therapeutic intervention in cancer.

Collectively, ACBI3, ACBI4, and MCB-36 exemplify concerted scientific efforts to develop a universal therapeutic strategy against oncogenic KRAS. The overarching premise of this approach is that complete degradation of KRAS protein offers superior efficacy because of catalytic inhibition. However, the primary clinical challenge remains the management of on-target toxicities resulting from the essential physiological roles of wild-type KRAS in normal tissue homeostasis. Achieving a sufficient therapeutic index through tumor-selective degradation or careful dosing schedules will be essential. Together, these 3 compounds not only illuminate a path toward successful targeting of KRAS degradation but also serve as indispensable tools for addressing these critical translational questions.

Clinical implications and future directions

Pan-KRAS inhibitors are entering clinical trials and may offer a much-needed therapeutic option for patients with non-G12C KRAS mutations. This advance is rooted in the distinct biochemical profiles of different KRAS mutants. Whereas some mutants, such as G12C, can be targeted with nucleotide-state-dependent drugs, others, such as G12R and Q61H/K, have impaired nucleotide cycling and are better addressed by strategies such as targeted protein degradation. These insights are driving a shift from mutation-specific to mutation-agnostic therapies, in a critical evolution in targeting *KRAS*-driven cancers. However, the clinical translation of candidates such as MCB-294 and ACBI3 faces several interconnected challenges. A primary concern remains achieving high selectivity for mutant KRAS over the wild-type protein and other RAS isoforms, which is essential to minimize on-target/off-tumor toxicity and ensure a viable therapeutic index. These selectivity challenges are further compounded by compound-specific pharmacological limitations: the short half-life of MCB-294 (~1.1 h in mice) necessitates twice-daily dosing, whereas ACBI3's current reliance on parenteral administration is a clear drawback with respect to oral agents. Beyond toxicity and pharmacokinetics, the success of these agents will depend on the development of robust predictive biomarkers transcending simple KRAS mutation status. The identification of KRAS dependency signatures and the elucidation of mechanisms of acquired resistance, such as upstream RTK reactivation or adaptive changes in parallel pathways, will be critical for effective patient selection. Furthermore, rationally designed combination regimens will be key to enhancing the depth and durability of treatment responses. Strategies may include vertical pathway inhibition targeting nodes such as SHP2 or EGFR, particularly in CRC and NSCLC, as well as immunotherapy combinations with anti-PD-1 agents. Immunotherapy combinations may be particularly relevant in immunologically cold tumors such as pancreatic ductal adenocarcinoma, in which KRAS inhibition has been shown to promote T-cell infiltration and to potentially sensitize tumors to immune checkpoint blockade.

Future research efforts should prioritize the elucidation of on-target resistance mechanisms unique to pan-KRAS inhibition, including point mutations at allosteric binding sites, KRAS amplification, or conformational adaptive changes. The development of next-generation inhibitors capable of countering these escape pathways will be essential. Integrating advanced techniques in structural biology, functional genomics, and patient-derived organoid/xenograft models has

potential to accelerate the translation of pan-KRAS targeting agents from bench to bedside and ultimately improve outcomes for patients with diverse *KRAS*-altered malignancies.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xiufeng Pang.
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