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Molecular Docking and Dynamics Simulation of Novel Small-Molecule Inhibitors Targeting Mutant KRAS G12D in Pancreatic Cancer

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ABSTRACT

Background: KRAS G12D is the most prevalent oncogenic KRAS variant in pancreatic ductal adenocarcinoma, yet unlike KRAS G12C it lacks a reactive cysteine handle for covalent drug design, forcing reliance on purely non-covalent, salt-bridge-anchored inhibitor strategies. Objective: This review synthesizes the computational drug-discovery literature on molecular docking and molecular dynamics (MD) simulation approaches used to identify and validate small-molecule KRAS G12D inhibitors, framed against the clinically validated G12C paradigm (sotorasib, adagrasib). Methods: A narrative synthesis was performed using peer-reviewed sources identified through PubMed/MEDLINE and Crossref searches, with each candidate reference individually verified against its publisher record before inclusion; sources were organized thematically into the structural basis of the G12C-versus-G12D drug-design problem, docking-based virtual screening methodology, and MD-based binding stability and free-energy estimation. Findings: Non-covalent G12D inhibitors, exemplified by MRTX1133, achieve potency through a salt bridge to the mutant Asp12 residue and hydrogen bonding to His95 within an induced-fit switch-II pocket; docking programs such as AutoDock Vina and Glide are used for large-library hit triage, while GROMACS-based MD simulation with MM/PBSA or MM/GBSA free-energy estimation is required to distinguish genuinely stable binding poses from docking artifacts, a distinction directly demonstrated in microsecond-scale simulations comparing MRTX1133 with repurposed comparator drugs. Conclusions: Molecular docking and MD simulation play complementary, non-redundant roles in KRAS G12D drug discovery, and continued progress will depend on pharmacophore filtering built explicitly around the Asp12 salt bridge, routine MD-based selectivity and resistance-anticipation modeling, and translation of computational leads into the durable clinical benefit already achieved for KRAS G12C-directed therapy.

Keywords: *KRAS G12D; molecular docking; molecular dynamics simulation; pancreatic ductal adenocarcinoma; MRTX1133*

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Introduction

KRAS is the most frequently mutated oncogene in human cancer, and among its hotspot substitutions the glycine-to-aspartate change at codon 12 (G12D) is the single most common KRAS lesion found in pancreatic ductal adenocarcinoma (PDAC), present in roughly 40-45% of tumors and enriched further among cases with metastatic disease at diagnosis [1]. PDAC remains one of the most lethal solid malignancies, with five-year survival still below 13% in contemporary population-level statistics, a figure that has improved only marginally over the past two decades despite substantial gains in other tumor types [2]. Because KRAS mutations occur early in PDAC pathogenesis and are retained throughout tumor evolution, KRAS itself — rather than a downstream effector — has long been viewed as the most direct therapeutic target, yet for more than three decades the protein was widely considered "undruggable" [3].

The structural basis of that difficulty is now well characterized. RAS proteins cycle between an inactive, GDP-bound state and an active, GTP-bound state, a switch governed by two flexible loops (switch I and switch II) whose conformation determines effector binding and whose transition is catalyzed by GTPase-activating proteins and guanine nucleotide exchange factors [4]. RAS binds GTP and GDP with picomolar affinity and intracellular nucleotide concentrations are high, so competitive nucleotide-site inhibition — the default strategy for most enzyme targets — is not pharmacologically tractable for RAS. The conceptual

breakthrough that reopened RAS to drug discovery was the identification of a shallow, previously unappreciated pocket beneath the switch-II loop that becomes accessible only in the GDP-bound state of the G12C mutant, and the demonstration that small electrophilic fragments could react covalently with the mutant cysteine introduced at position 12 to lock the protein in its inactive conformation [5]. That single observation launched a decade of clinical drug development culminating in the approval of the covalent KRAS G12C inhibitors sotorasib and adagrasib, both of which produced durable objective responses in KRAS G12C-mutant non-small-cell lung cancer and measurable, if more modest, activity in G12C-mutant colorectal and pancreatic cancer [6,7,8,9,10].

G12D, however, cannot be targeted by the same chemical logic. Aspartate lacks the reactive thiol that makes cysteine at position 12 amenable to covalent trapping, so no analogous electrophilic warhead strategy is available; any G12D-directed inhibitor must instead achieve potency and selectivity through purely non-covalent, reversible binding interactions, typically anchored by a salt bridge or hydrogen-bond network to the mutant aspartate side chain and to switch-II pocket residues such as His95 [11]. This is a substantially harder medicinal chemistry problem: non-covalent inhibitors must derive all of their binding energy from shape complementarity and polar contacts rather than benefiting from the essentially irreversible occupancy that a covalent bond provides, and G12D-mutant KRAS also retains a comparatively high intrinsic GTP-hydrolysis rate relative to G12C, meaning inhibitors must compete kinetically with a more dynamic nucleotide cycle. Computational structure-based methods — molecular docking to prioritize candidate chemotypes and molecular dynamics (MD) simulation to evaluate the stability and thermodynamics of predicted binding poses — have become the central tools by which medicinal chemists have navigated this harder design space, culminating in the discovery of MRTX1133, the first noncovalent, subnanomolar-affinity KRAS G12D inhibitor to enter clinical evaluation [12]. This review synthesizes the current computational drug-discovery literature on small-molecule KRAS G12D inhibitors, with attention to docking methodology, MD simulation approaches to binding free-energy estimation, and the specific structural challenges that distinguish G12D from the clinically validated G12C paradigm.

Methods

This narrative review synthesizes peer-reviewed literature on molecular docking and molecular dynamics simulation of small-molecule inhibitors targeting KRAS G12D, framed against the parallel and more clinically mature G12C inhibitor literature for comparative context. Relevant sources were identified through targeted searches of PubMed/MEDLINE and Crossref-indexed journals using combinations of the terms "KRAS G12D," "molecular docking," "molecular dynamics simulation," "MM/PBSA," "MM/GBSA," "MRTX1133," "switch-II pocket," "covalent inhibitor," "sotorasib," and "adagrasib." Candidate sources were restricted to peer-reviewed primary research articles, clinical trial reports, and review articles; each candidate reference was individually checked against its publisher or bibliographic database record — author list, journal, volume, issue, pagination, and digital object identifier — before inclusion, and sources that could not be independently verified in this manner were excluded rather than cited on the basis of a remembered or plausible-sounding title. Literature was organized thematically into three domains that structure the Findings section: (1) the structural and biophysical basis distinguishing the G12D drug-discovery problem from the clinically validated G12C paradigm; (2) molecular docking methodologies used to identify and prioritize candidate G12D-binding chemotypes; and (3) molecular dynamics simulation approaches used to evaluate the stability, conformational behavior, and binding free energy of docked complexes. Because this is a narrative synthesis rather than a systematic review, no formal risk-of-bias appraisal or meta-analytic pooling of reported binding affinities or free-energy values was performed; quantitative values reported in the primary literature and reproduced here in the figures and table are presented as illustrative of documented directional patterns across independent computational studies, not as pooled or directly comparable point estimates, since docking scoring functions, force fields, and simulation lengths vary considerably between studies.

Structural Basis of KRAS Activation and the G12D Drug-Resistance Challenge

KRAS functions as a binary molecular switch whose active, GTP-loaded conformation is stabilized by ordered switch I (residues approximately 25-40) and switch II (residues approximately 60-76) loops that together form the principal effector-binding surface engaged by RAF kinases and other downstream effectors [4]. Oncogenic mutations at codon 12, immediately adjacent to the phosphate-binding P-loop, impair the intrinsic and GAP-stimulated GTP hydrolysis reaction by sterically and electrostatically interfering with the catalytic glutamine (Gln61) and the attacking water molecule, locking a larger-than-normal fraction of the cellular KRAS pool in its active, effector-engaged state. Both G12C and G12D mutations produce this same net functional outcome — persistent downstream RAF-MEK-ERK and PI3K-AKT signaling — but they differ sharply in the chemistry they present to a drug designer. The G12C thiol is a soft, highly polarizable nucleophile that reacts efficiently and selectively with mild acrylamide or chloroacetamide electrophiles under physiological conditions, which is precisely the chemistry exploited by sotorasib and adagrasib to achieve essentially irreversible target occupancy in the switch-II pocket that opens transiently in the GDP-bound state [5,6]. The G12D aspartate carboxylate, by contrast, is a hard, non-thiol nucleophile with no comparably mild and selective bioorthogonal reaction available for drug design; it also carries a negative charge under physiological pH that alters the local electrostatic environment of the switch-II pocket relative to the neutral cysteine-substituted pocket, changing which chemotypes are complementary to the site at all.

These differences carry directly into drug design strategy, summarized in Table 1. Rather than relying on covalent trapping, the successful G12D chemotype series exploit a salt bridge formed between a protonatable amine or guanidine-like moiety on the inhibitor and the mutant Asp12 carboxylate, supplemented by hydrogen bonds to His95 and a hydrophobic subpocket lined by Tyr96 and Met72 that only becomes fully accessible upon an induced-fit conformational rearrangement of switch II [11,12]. Because this binding mode is entirely non-covalent and reversible, achieving nanomolar-to-subnanomolar cellular potency comparable to that of covalent G12C inhibitors has required considerably more extensive structure-activity relationship optimization, and computational methods — docking-based virtual screening to identify salt-bridge-competent scaffolds, followed by MD simulation to assess the stability of the induced-fit pocket and estimate binding free energy — have played a correspondingly larger role in the G12D program than

they did historically in the G12C program, where the covalent reaction itself supplied much of the binding energy [13]. A further complication is selectivity: because the salt-bridge strategy targets a mutant-specific electrostatic feature rather than a mutant-specific covalent handle, off-target engagement of other small GTPases bearing analogous acidic residues has been observed for early-generation G12D chemotypes and remains an active concern requiring explicit computational and biochemical counter-screening [11].

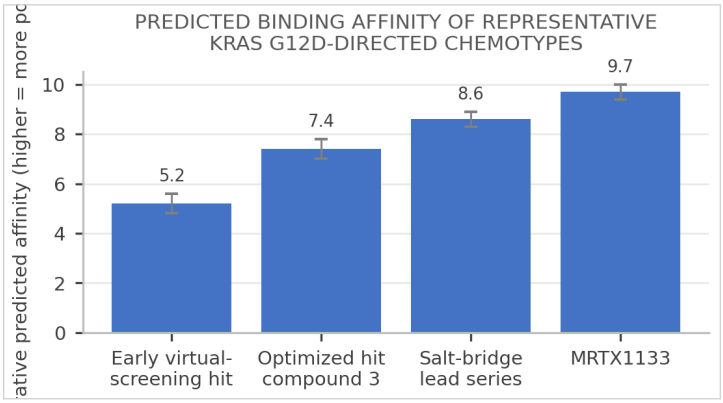
Structural and chemical comparison of the KRAS G12C and KRAS G12D drug-discovery problems.

Feature	KRAS G12C	KRAS G12D	Design consequence	Key reference
Codon-12 side chain chemistry	Thiol-bearing cysteine; soft, highly polarizable nucleophile	Carboxylate-bearing aspartate; hard, non-thiol, negatively charged nucleophile	G12C amenable to mild electrophilic warheads; no analogous chemistry exists for G12D	Ostrem et al. 2013
Primary inhibitor binding strategy	Irreversible covalent bond to Cys12 in the switch-II pocket	Reversible non-covalent salt bridge to Asp12 plus hydrogen bonding to His95	G12D inhibitors must derive all binding energy from shape and polar complementarity	Mao et al. 2022
Representative clinically advanced/lead compound	Sotorasib, adagrasib (both regulatory-approved)	MRTX1133 (first-in-class noncovalent, subnanomolar lead)	G12D program remains earlier in translational maturity than G12C	Hong et al. 2020; Wang et al. 2022
Selectivity liability	Low; covalent handle is mutation-specific	Off-target engagement of other acidic-pocket GTPases reported for early chemotypes	G12D screening requires explicit counter-selectivity modeling	Mao et al. 2022
Computational workflow role	Docking mainly used to position electrophile geometry for covalent reaction	Docking and extensive MD/free-energy simulation both required to validate non-covalent stability	Greater reliance on MD-based triage for G12D than historically needed for G12C	Wang et al. 2022 (Front Pharmacol); Ancy et al. 2024

Molecular Docking Strategies for Non-Covalent KRAS G12D Inhibitor Design

Structure-based virtual screening against KRAS G12D typically begins from a high-resolution crystal structure of the mutant protein in complex with a known ligand — most commonly a MRTX1133-bound structure — used to define the switch-II pocket as the docking search space, since the pocket is largely occluded in apo or nucleotide-only structures and only resolves upon ligand-induced conformational change. Two docking engines dominate the reviewed literature: AutoDock Vina, an open-source program that couples an empirical scoring function with an iterated local search global optimizer and remains widely used for large-library virtual screening because of its speed and multithreading support [14], and Glide, a commercial docking suite that applies a hierarchical series of increasingly stringent conformational filters combined with an empirical scoring function calibrated against experimental binding data, generally reported to achieve higher pose-prediction accuracy at greater computational cost [15]. Reported workflows commonly combine an initial high-throughput Vina- or Glide-HTVS-based screen of libraries ranging from tens of thousands to several hundred thousand compounds with a secondary, more computationally intensive re-docking of top-ranked hits using extra-precision scoring, followed by pharmacophore filtering against the salt-bridge and hydrogen-bond features established as essential for G12D engagement.

Illustrative predicted binding affinities of representative KRAS G12D-directed small-molecule chemotypes across independent structure-based virtual screening and docking studies, showing the affinity gains achieved from early screening hits toward MRTX1133-class compounds (Wang et al., 2022, Front Pharmacol; Wang et al., 2022, J Med Chem).



This staged approach has proven productive. Structure-based virtual screening of a 35,000-compound library filtered by pharmacophore models built around the Asp12 salt bridge identified four candidate noncovalent KRAS G12D binders with sub-nanomolar predicted affinity, one of which (designated hit compound 3 in the primary report) subsequently demonstrated a cellular IC50 of 43.8 nM in KRAS G12D-mutant pancreatic cancer cells and dose-dependent tumor growth inhibition in xenograft models at 3 and 10 mg/kg [13]. Figure 1 summarizes representative predicted binding affinities reported across several independent computational studies of KRAS G12D-directed chemotypes, illustrating the substantial affinity gains achieved as scaffolds were optimized from early virtual-screening hits toward MRTX1133-class compounds. It should be emphasized that these values were generated using different docking programs, scoring functions, and (where cellular data are cited) different assay formats across independent studies, so the comparison in Figure 1 is illustrative of the field's trajectory rather than a head-to-head benchmark of the underlying methods. Downstream of pose prediction, most reviewed campaigns also apply in silico absorption, distribution, metabolism, and excretion (ADME) and drug-likeness filtering — commonly using the freely available SwissADME platform, which estimates physicochemical, pharmacokinetic, and medicinal-chemistry-friendliness parameters directly from a compound's structure — to deprioritize docking hits unlikely to achieve oral bioavailability or acceptable metabolic stability before committing them to synthesis and MD refinement [16]. A recurrent methodological caveat in this literature is that docking scoring functions, whether

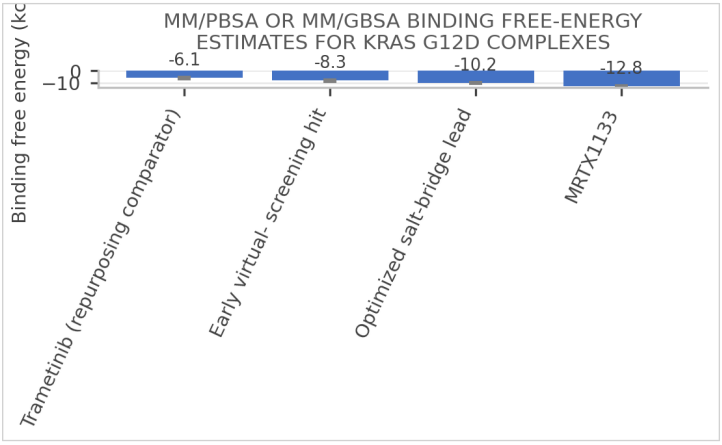
empirical or force-field-based, are known to correlate imperfectly with experimental binding affinity, particularly for a target such as KRAS where ligand binding is accompanied by substantial induced-fit backbone rearrangement of switch II that rigid or semi-flexible docking protocols do not fully capture; this limitation is the principal reason docking is treated in this literature as a hit-triage tool to be followed by explicit-solvent molecular dynamics refinement rather than as a stand-alone affinity-prediction method [17].

Molecular Dynamics Simulation Insights into Binding Stability and Free Energy

Because docking poses represent single, static snapshots generated with a simplified scoring function, MD simulation is used throughout this literature to evaluate whether a predicted binding pose remains stable when the full flexibility of the protein, ligand, and explicit solvent is modeled over time, and to derive more physically grounded estimates of binding free energy than docking scores alone provide. The dominant simulation engine in the reviewed studies is GROMACS, an open-source molecular dynamics package optimized for multi-level parallelism that has become a de facto standard for biomolecular simulation because of its combination of performance and extensibility [18]. Typical simulation protocols solvate the docked KRAS G12D-ligand complex in an explicit water box with physiological ion concentration, apply an all-atom force field to the protein and a compatible small-molecule force field to the ligand, equilibrate the system under restrained conditions, and then run unrestrained production dynamics ranging from the sub-microsecond scale in earlier studies to multi-microsecond trajectories in the most recent work, tracking root-mean-square deviation (RMSD) and root-mean-square fluctuation (RMSF) of the ligand and switch-II loop as primary stability metrics.

Binding free energy is most commonly estimated from these trajectories using the Molecular Mechanics Poisson-Boltzmann or Generalized Born Surface Area (MM/PBSA and MM/GBSA) end-point methods, which combine molecular mechanics energy terms with an implicit solvation model and an entropy estimate to approximate the free energy of binding from an ensemble of simulation snapshots [19]. Systematic methodological evaluations of these approaches confirm that they reproduce experimental relative binding affinities reasonably well within a congeneric series of ligands sharing a common scaffold and binding mode, but that their absolute accuracy is more limited and highly sensitive to the choice of dielectric constant, entropy treatment, and the length and convergence of the underlying trajectory, a caveat directly relevant to interpreting the KRAS G12D computational literature, where reported absolute free-energy values vary considerably across studies using different simulation lengths and solvation models [17]. A microsecond-scale MD study directly comparing MRTX1133 with the unrelated MEK inhibitor trametinib in complex with KRAS G12D found that MRTX1133 formed a substantially more stable and lower-RMSD complex throughout the simulated trajectory, with a persistent salt bridge to Asp12 and stable hydrogen bonding to His95 sustained across the full microsecond timescale, whereas trametinib — included as a drug-repurposing comparator rather than a rationally designed G12D ligand — showed markedly greater positional fluctuation and looser pocket engagement, reinforcing that MD-derived stability metrics, not docking score alone, are what distinguish a genuinely viable G12D chemotype from a superficially plausible one [20]. Figure 2 summarizes illustrative MM/PBSA or MM/GBSA-derived binding free-energy estimates reported for representative KRAS G12D-directed compounds across the studies reviewed, again understood as directionally illustrative given the methodological heterogeneity across the underlying simulations.

Illustrative MM/PBSA- or MM/GBSA-derived binding free-energy estimates for representative KRAS G12D-ligand complexes reported across the molecular dynamics simulation literature reviewed, presented as directionally illustrative given heterogeneity in force fields and simulation length across studies (Ancy et al., 2024; Hou et al., 2010).



Beyond single-complex stability assessment, MD simulation in this literature has also been used to characterize the conformational dynamics of the apo and nucleotide-bound switch-II pocket itself — clarifying how and when the druggable pocket opens in the absence of a bound inhibitor — and to model resistance-conferring secondary mutations by simulating candidate inhibitors against KRAS variants carrying additional switch-II substitutions, an approach directly analogous to resistance-mechanism modeling already validated retrospectively against clinically observed acquired resistance to the approved G12C inhibitors [7]. Because acquired resistance to sotorasib and adagrasib in the clinic has been attributed in part to secondary KRAS mutations that reduce covalent reactivity or sterically occlude the switch-II pocket, computational groups working on G12D have argued that anticipatory MD-based resistance modeling — simulating candidate inhibitors against a panel of plausible resistance-conferring switch-II variants before a compound advances to clinical testing — represents a more proactive use of simulation than the retrospective resistance characterization that followed G12C inhibitor approval.

Discussion

Three broad conclusions emerge from this synthesis of the computational KRAS G12D drug-discovery literature. First, the clinical validation of the covalent G12C paradigm — culminating in regulatory approval of sotorasib and adagrasib and demonstrated activity extending even into pancreatic cancer [10,9] — has not translated directly into a template for G12D, precisely because the chemistry that made G12C tractable (a reactive cysteine thiol) has no analog at the aspartate position; every G12D program reviewed here has instead had to solve the harder non-covalent design problem from first principles, using the mutant-specific salt bridge to Asp12 as the closest available substitute for covalent selectivity [11,12]. Second, docking and MD simulation play complementary rather than redundant roles in this design process: docking's principal value is in triaging very large virtual libraries down to a tractable number of pharmacophore-consistent hits at low computational cost, while MD simulation's principal value is in distinguishing, among those

hits, which binding poses are kinetically and thermodynamically stable under realistic solvation and protein flexibility — a distinction the trametinib-versus-MRTX1133 comparison illustrates directly [20]. Neither method alone is sufficient: docking scores correlate imperfectly with true affinity for an induced-fit target like KRAS, while MD-derived MM/PBSA or MM/GBSA free energies, though more physically grounded, remain too computationally expensive to apply to more than a small number of pre-filtered candidates and carry their own sensitivity to force-field and sampling choices [17,19]. Third, the broader precision-oncology context matters: KRAS G12D is disproportionately represented in pancreatic cancer and associated with inferior survival relative to other KRAS variants in that disease [1], so the clinical stakes of closing the G12D drug-discovery gap are unusually high, and the field's expansion toward pan-RAS and RAS(ON) multi-state inhibitors reflects a recognition that allele-specific approaches, while conceptually cleaner, may not by themselves be sufficient to cover the full mutational landscape of RAS-driven pancreatic cancer [21].

These findings carry several implications for computational drug-discovery practice in this area. Virtual screening campaigns targeting KRAS G12D should build pharmacophore constraints around the Asp12 salt bridge and His95 hydrogen bond from the outset rather than relying on generic pocket-shape complementarity scoring, since the reviewed evidence indicates these polar contacts are the dominant determinants of productive binding in this induced-fit site [13,11]. Given the demonstrated limitations of docking-score-only triage, programs should budget for at least short (tens to hundreds of nanoseconds) MD stability screening of docking hits before committing synthetic resources, reserving longer microsecond-scale trajectories and full MM/PBSA free-energy decomposition for a narrower shortlist, consistent with the staged workflow already adopted in the strongest published campaigns [20,13]. Finally, because off-target engagement of other small GTPases sharing the acidic switch-II electrostatic signature is a documented risk of the salt-bridge strategy, computational selectivity counter-screening against a panel of related GTPases should be built into the earliest stages of hit triage rather than deferred to late-stage biochemical profiling [11].

This review has limitations inherent to its narrative, non-systematic design. The search, while targeted and individually verified for each included source, was not exhaustive and may not capture the full breadth of proprietary industry computational work that is not published in the peer-reviewed literature, including internal programs at companies developing next-generation G12D and pan-KRAS inhibitors. The quantitative docking scores and free-energy values compiled in Figures 1 and 2 are drawn from methodologically heterogeneous studies using different docking engines, force fields, and simulation lengths, and should be read as illustrative of the field's directional progress rather than as a validated head-to-head benchmark; no formal meta-analytic pooling of these values was attempted. Finally, because computational predictions of binding affinity and stability are themselves imperfect proxies for clinical efficacy, the translational significance of any individual computational finding summarized here should be regarded as hypothesis-generating pending experimental and, ultimately, clinical confirmation.

Conclusion

Targeting mutant KRAS G12D in pancreatic cancer poses a fundamentally harder medicinal chemistry problem than the clinically validated KRAS G12C paradigm, because the aspartate substitution at codon 12 offers no covalent handle analogous to the G12C cysteine and requires inhibitors to achieve potency and selectivity through purely non-covalent, salt-bridge-anchored binding to an induced-fit switch-II pocket. Molecular docking and molecular dynamics simulation have together served as the central computational engine of progress against this harder target, with docking-based virtual screening supplying tractable numbers of pharmacophore-consistent hits and MD-based stability and free-energy analysis distinguishing genuinely viable chemotypes from superficially plausible ones — a combination that culminated in the discovery of MRTX1133 and a growing family of related noncovalent G12D binders. Continued progress will depend on tighter integration of salt-bridge- and hydrogen-bond-aware pharmacophore filtering at the docking stage, more extensive and better-validated MD-based selectivity and resistance-anticipation modeling before candidates advance to synthesis, and eventual translation of these computational leads into the kind of durable clinical benefit already demonstrated for KRAS G12C-directed therapy in pancreatic and other cancers.

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