MILESTONE 12

Undruggable? Inconceivable

In the cult-classic film *The Princess Bride*, every time the Man in Black (the good guy) overcomes an insurmountable obstacle, Vizzini (the bad guy) exclaims, "Inconceivable!" This happens repeatedly, until eventually Vizzini's companion tells him, in a moment of comedic perfection, "You keep using that word. I do not think it means what you think it means."

So it was with 'undruggable' RAS. In the early 2000s, when dozens of kinase inhibitors were heading to the clinic, comparatively little progress was being made on key non-kinase targets in oncology. RAS, a small GTPase, is one of the most frequently altered proteins in cancer and was therefore pursued with particular fervour. The lack of success in identifying RAS inhibitors led many to call it undruggable.

Credit: Lobo36

Then, in 2013, Kevin Shokat's lab developed a groundbreaking inhibitor of the KRAS G12C mutant, one of the most prevalent RAS alterations in non–small cell lung cancer (NSCLC). Shokat's compound forms a covalent bond with the inherently reactive cysteine residue at position 12 in the altered form of RAS, whereas wild-type RAS has a glycine in this position and does not react with Shokat's compound.

This discovery formed the basis of Wellspring Biosciences, which turned the compound into a more drug-like molecule, ARS-1620. From this growing field of covalent RAS inhibitors, two drugs have since been developed and shown signs of efficacy in early-stage clinical trials: Amgen's sotorasib (AMG510) and Mirati's MRTX849.

Both sotorasib and MRTX849 form covalent bonds with the reactive cysteine in KRAS-G12C. In mouse models of cancers driven by KRAS-G12C, these agents induce tumour regression as monotherapies. Their anticancer activity is enhanced when they are combined with other chemotherapeutic agents (particularly those that inhibit kinases downstream of RAS) or, for sotorasib, with checkpoint inhibitors.

In the phase I trial of AMG510, no dose-limiting toxic effects or treatment-related deaths were observed. In patients with NSCLC or colorectal cancer, disease control (stable disease or an objective response) occurred in 88% or 74% respectively, of this small patient group. The extent of efficacy of MRTX849 and AMG510 will be determined in ongoing and future larger clinical trials.

RAS cycles between GTP-bound and GDP-bound states. Unexpectedly, the G12C inhibitors bind the GDP-bound, inactive state, thus demonstrating that KRAS G12C is not constitutively active (as previously thought) but is hyperexcitable. This key insight into RAS biology was enabled by the covalent inhibitors and spurred investigations into state-specific RAS-binding compounds.

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Not all RAS alterations are G12C, and efforts are underway to find compounds that inhibit non-G12C RAS alterations. Different tumour types tend to have different *RAS* mutations—although nearly half the RAS alterations found in lung cancer are G12C, the G12D alteration is more prevalent in pancreatic and colon cancers.

One of the more promising pan-mutation approaches is to target the interactions between RAS and either its downstream effectors or SOS, a guanine-nucleotide-exchange factor that activates RAS. Genentech, Boehringer Ingelheim and academic researchers including Terence Rabbitts have used structure-based design to identify compounds that inhibit these interactions and thus downstream signalling. Indeed, the Boehringer Ingelheim compound also decreases the growth of NSCLC cells with *RAS* mutations.

Compounds that inhibit multiple forms of RAS could have toxic, on-target effects in non-cancerous cells. Evidence from preclinical studies, however, suggests that differences in affinity for wild-type versus mutant RAS could provide a therapeutic window for these compounds.

Compounds targeting KRAS isoforms other than G12C that are commonly found in NSCLC, pancreatic cancer and colorectal cancer are also in development. These compounds may avoid the toxicities that could arise from pan-mutation RAS inhibitors.

Efforts to find inhibitors for other non-kinase targets have had less success than those for RAS. p53, another lucrative anticancer target, remains clinically untamed. Indeed, the nutlins, a much-lauded group of potential p53-inhibitory compounds from Roche, failed in a phase III trial in acute myeloid leukaemia in mid-2020. MYC, also high on the list of cancer targets, remains undrugged.

Targeted degradation could be useful for these other undruggable proteins. Proteolysis-targeting chimeras (PROTACs) serve as synthetic E3 ligases, which bind target proteins and mark them for ubiquitin-mediated degradation. Originally conceived in Craig Crews's lab in 2001, the first PROTAC, which induces degradation of the androgen receptor, successfully completed a phase I trial in 2020, showing some signs of antitumour efficacy.

Although many non-kinase cancer targets remain undrugged, the success of covalent KRAS inhibitors and PROTACs demonstrates that developing therapeutic compounds that target these proteins may be not only conceivable but also well within the range of current possibilities.

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ORIGINAL ARTICLE Ostrem, J. et al. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature* **503**, 548–551 (2013).
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