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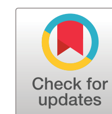

Targeting the "undruggable" cancer driver genes: *Ras*, *myc*, and *tp53*

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Abstract: The term "undruggable" is to describe molecules that are not targetable or at least hard to target pharmacologically. Unfortunately, some targets with potent oncogenic activity fall into this category, and currently little is known about how to solve this problem, which largely hampered drug research on human cancers. *Ras*, as one of the most common oncogenes, was previously considered "undruggable", but in recent years, a few small molecules like Sotorasib (AMG-510) have emerged and proved their targeted anti-cancer effects. Further, *myc*, as one of the most studied oncogenes, and *tp53*, being the most common tumor suppressor genes, are both considered "undruggable". Many attempts have been made to target these "undruggable" targets, but little progress has been made yet. This article summarizes the current progress of direct and indirect targeting approaches for *ras*, *myc*, two oncogenes, and *tp53*, a tumor suppressor gene. These are potential therapeutic targets but are considered "undruggable". We conclude with some emerging research approaches like proteolysis targeting chimeras (PROTACs), cancer vaccines, and artificial intelligence (AI)-based drug discovery, which might provide new cues for cancer intervention. Therefore, this review sets out to clarify the current status of targeted anti-cancer drug research, and the insights gained from this review may be of assistance to learn from experience and find new ideas in developing new chemicals that directly target such "undruggable" molecules.

Introduction

Targeted therapy is one of the major modalities of medical treatment for cancer, which blocks the growth of cancer cells by interfering with specific target molecules.

Multiple targeting drugs are available for several exhaustively studied oncogenes. For example, for epidermal growth factor receptor (*egfr*) gene-activating mutations that occur in about 15% of lung adenocarcinomas, at least 3 generations of the US Food and Drug Administration (FDA) approved EGFR inhibitors are available with several more undergoing clinical trials (Cooper *et al.*, 2022).

However, currently approved treatments are available for only a small fraction of approximately 700 identified cancer genes (Sondka *et al.*, 2018). As a consequence, we still lack valid treatments for the vast majority of cancer-causing genes, including some of those that are most frequently altered.

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Ras, *myc*, and *tp53* are the most frequently altered cancer-driving genes as highly attractive targets for cancer treatment (Leroy *et al.*, 2014; Simanshu *et al.*, 2017; Priestley *et al.*, 2019). However, the protein products of each of these genes are difficult to target. Therefore, these highly studied but poorly targeted cancer-driver genes have traditionally been referred to as "undruggable" (Dang *et al.*, 2017). RAS, MYC, and P53 are difficult to be targeted by drugs for the following four reasons. First, all these proteins lack a deep protein binding pocket, which is a cavity on the surface or inside of a protein with ligand-binding properties, whose shape and position in the protein and the sequence of the surrounding amino acid residues determine its function (Stank *et al.*, 2016). Second, protein-protein interactions (PPIs) of these proteins are only through large and flat interfaces (Dang *et al.*, 2017; Tsubamoto *et al.*, 2019). Targeting the biological functions of these genes is rather difficult because PPIs are indispensable for most of their genetic functions (Athanasios *et al.*, 2017). Third, all three proteins are located intracellularly, that is, while RAS is present on the inner layer of the cell membrane, both MYC and P53 are in the nucleus. Consequently, the size of the

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drug molecule is strictly restrained. Finally, except for RAS, both MYC, and P53 lack enzymatic activity. Thus, their targeting cannot be performed by catalytic inhibitors.

Biology of Ras

The *ras* family of genes consists of three members, *k-ras*, *n-ras*, and *h-ras*. RAS proteins play the role of "binary switch" in cellular signaling pathways by cycling between an active state and an inactive state (Vigil *et al.*, 2010). The guanylate exchange cycle plays a decisive role in the activation of RAS proteins. GTP-bound RAS protein is activated whereas GDP-bound RAS protein is inactivated (Pylayeva-Gupta *et al.*, 2011; Stephen *et al.*, 2014). RAS proteins have GTPase activity, which is enhanced by RAS GTPase activating protein (RAS GAP), turning the RAS protein from the activated (GTP-bound) form back to the inactivated state (GDP-bound) (Lito *et al.*, 2016). RAS guanine nucleotide exchange factor (RAS GEF) plays a role in catalyzing the ejection of GTPase-bound GDP and the loading of GTP, thereby meditating the activation of RAS proteins (Rossman *et al.*, 2005). For membrane localization of RAS proteins, post-translational modifications (PTMs) are necessary. PTMs are catalyzed by farnesyl transferase (FTase), geranylgeranyl transferase (GGTase), RAS-converting enzyme (Rce1), and isoprenylcysteine carboxyl methyltransferase (ICMT) (Moore *et al.*, 2020). After being processed by PTMs, RAS proteins undergo oligomerization. To elaborate, RAS proteins assemble on the plasma membrane as nanoclusters or dimers, which act as recruitment and activation sites for downstream RAS effector molecules (Šolman *et al.*, 2015; Zhou and Hancock, 2015).

Ras mutations in cancer

About 30% of human cancers have mutations in the *ras* family (*k-ras*, *n-ras*, and *h-ras*), which can cause persistent activity of RAS proteins (Cox *et al.*, 2014; Simanshu *et al.*, 2017). Besides, a large proportion of drug-resistant tumors activate the RAS pathway to overcome the effects of kinase inhibitors (Massarelli *et al.*, 2007). Among all 3 forms of *ras*, *k-ras* is the most frequently mutated in human cancers (85%), followed by *n-ras* (12%) and *h-ras* (3%) (Simanshu *et al.*, 2017). Frequencies of mutations in *ras* isoforms vary in different tissues. For example, *k-ras* is most frequently mutated in the pancreas (91%), colon (42%), and lung (33%) while *n-ras* is most frequently mutated in the skin, especially in melanoma (27%), bone marrow (8%) and thyroid (8%) and *h-ras* is most frequently mutated in adrenal glands (10%), thymus (8%) and bladder (5%) (Simanshu *et al.*, 2017). Most *ras* mutations are found in codons 12, 13, or 61, corresponding to glycine 12 (G12), glycine 13 (G13), or glutamine 61 (Q61), respectively (Simanshu *et al.*, 2017; Asimgil *et al.*, 2022).

Biology of myc

The *myc* family consists of 3 members, *c-myc*, *l-myc*, and *n-myc*. All three MYC proteins function as transcriptional regulators, which can integrate multiple cellular signals and regulate the expression of genes involved in multiple biological processes that are essential to normal as well as neoplastic cells, such as cell proliferation, metabolism, differentiation, DNA repair, immune response and apoptosis (Carroll *et al.*, 2018; Casey *et al.*, 2018; Singh *et al.*, 2019). To regulate gene expression programs like growth, proliferation, differentiation, apoptosis, and metabolism, the MYC protein employs its basic-helix-loop-helix-zipper (bHLHZ) domain to form the heterodimer "MYC-MAX" with the bHLHZ domains of the MAX protein. Similarly, MAX also forms heterodimers with the MXD family (as well as MNT and MGA proteins) via the bHLHZ domains to form what is known as "MXD-MAX". Both MYC-MAX and MXD-MAX directly bind to DNA regulatory sites, especially to canonical consensus 5′-CACGTG–3′ sequences located in E-box regions to perform their functions (Carroll *et al.*, 2018).

Myc and its deregulation in cancer

Myc genes are rarely mutated in contrast to *ras*. However, the *myc* family (*c-myc*, *l-myc*, *n-myc*) is one of the most commonly deregulated oncogenes in human cancers, which is estimated to be aberrantly expressed in up to 70% of human cancers (Llombart and Mansour, 2022). Some tumors activate *myc* expression, mediating resistance to targeted therapies (Dang, 2012; Elbadawy *et al.*, 2019). Among all 3 forms of *myc* genes, *c-myc* is the most frequently amplified gene (21%) across all cancer types. In contrast, *n-myc* and *l-myc* genes amplified less commonly (7%) at the pan-cancer level (Schaub *et al.*, 2018). Further, *c-myc* is most frequently amplified in ovarian serous cystadenocarcinoma (64.8%), esophageal carcinoma (45.3%), and lung squamous cell carcinoma (37.2%) (Schaub *et al.*, 2018). While *n-myc* and *l-myc* are less frequently amplified, *n-myc* amplification, however, has been documented in 20%–30% of neuroblastoma patients (Otte *et al.*, 2021).

Biology of tp53

In contrast to *ras* and *myc*, *tp53* is a tumor suppressor gene, which is frequently referred to as the "guardian of the genome" and functions to suppress cancer formation (Nguyen *et al.*, 2017; Binayke *et al.*, 2019; Janani *et al.*, 2021). Although discovered decades ago, the exact mechanism by which the *tp53* gene prevents cancer formation is still unclear. Wild type (WT) P53 acts as a transcription factor to regulate the expression of target genes that are involved in many distinct biological processes like cell cycle arrest and apoptosis (Kastan *et al.*, 1995; Fridman and Lowe, 2003). In normal unstressed cells, P53 protein levels are kept low and the biochemical activity of P53 is restrained. This is mainly attributed to the proteasomal degradation of P53 controlled by mouse double minute 2 (MDM2), which is an E3 ubiquitin ligase (Hassin and Oren, 2023).

Tp53 mutations in cancer

The *tp53* gene family is one of the most frequently mutated genes in human cancers with its mutation generally associated with poor prognosis (Leroy *et al.*, 2014; Kastenhuber and Lowe, 2017). For instance, across all human cancers, the overall mutational rate of *tp53* is about 50% (Levine, 2019). The frequency of *tp53* mutations varies

in different cancers. For example, *tp53* mutations are more likely to be found in malignancies such as ovarian cancers, lung cancers, and breast cancers (Cancer Genome Atlas Research Network, 2011; Cancer Genome Atlas Research Network, 2012; Cancer Genome Atlas Network, 2012; George *et al.*, 2015). Most *tp53* mutations are missense mutations, followed by nonsense mutations (Cai *et al.*, 2022).

We conclude this review with the current approaches and possible challenges of targeting *ras*, *myc*, *tp53* that are considered "undruggable". This review set out to clarify the current status of targeted anti-cancer drug research, and the insights gained from this review may be of assistance to learn from experience and find new ideas in developing new chemicals that target those "undruggable" molecules directly.

The Current Progress in Targeting *ras*, *myc*, and *tp53*

Ras inhibitors

In 2021, the FDA approved the first K-RAS inhibitor Sotorasib (AMG-510) (Mullard, 2022), which showed an overall response rate (ORR) (n = 124) of 36% [95% confidence interval (CI), 28–45] in patients with K-RAS-G12C-mutated non-small-cell lung cancer (NSCLC) (Nakajima *et al.*, 2022). Behind this achievement, tremendous efforts have been made by scientific workers on targeting RAS directly. The work of targeting K-RAS-G12C was started by Shokat and his colleagues, who identified a binding pocket Switch-II Pocket (S-IIP) in the mutated K-RAS-G12C protein (Ostrem *et al.*, 2013), which brought a turnaround in targeting K-RAS that was once thought to be undruggable. Based on this, many covalent inhibitors targeting K-RAS-G12C have entered clinical trials and even been approved for marketing, including Sotorasib (also AMG-510), Adagrasib (also MRTX849), JNJ-74699157 (also ARS-3248), LY3499446 and numerous other K-RAS-G12C inhibitors (Nagasaka *et al.*, 2020; Sidaway, 2021; Brazel *et al.*, 2022). Most of the current K-RAS-G12C inhibitors are only applicable for GDP-bound K-RAS-G12C proteins, which are RAS proteins in the inactivated state, whereas some recently developed K-RAS-G12C inhibitors, like RM-018, are valid for GTP-bound K-RAS-G12C proteins, which are RAS proteins in the activated state (Tanaka *et al.*, 2021). Additionally, non-specific RAS inhibitors are also being developed. While some of the RAS mutant proteins are specifically inhibited, it is currently difficult to identify effective treatments for each mutated RAS protein. Direct targeting of conserved ligand binding sites on all kinds of RAS proteins may provide a single therapeutic pathway to inhibit RAS across many mutations and tumor types. For example, compound 3144 targets the switch-I pocket, whereas compound Abd series, compound Ch series, and BI-2852 target the 4,6-dichloro-2-methyl-3-aminoethyl-indole (DCAI) pocket (Welsch *et al.*, 2017; Quevedo *et al.*, 2018; Cruz-Migoni *et al.*, 2019; Kessler *et al.*, 2019). However, the problem with this approach is that non-specific binding is highly toxic to healthy tissue cells as the RAS pathway is essential in cell signaling.

To target *ras* indirectly, past studies have mainly focused on the inhibition of RAS PTMs, oligomerization, nucleotide exchange, and downstream binding. Altering any of these basic steps could be a chance to inhibit *ras* indirectly.

Several enzymes catalyzing RAS PTMs are necessary for RAS membrane localization. These include FTase, GGTase, Rce1, and ICMT (Moore *et al.*, 2020). Inhibitors against each of these enzymes have the potential to be effective agents targeting RAS indirectly. In 2020, the FDA approved the first farnesyltransferase inhibitor, lonafarnib, for use as a treatment for Hutchinson-Gilford progeria syndrome and some progeroid laminopathies (Mullard, 2021). In addition, several more farnesyltransferase inhibitors are in clinical trials, such astipifarnib, L778123, BMS 214662, FTI-277, alpha-hydroxy farnesyl phosphonic acid, and manumycin-A (Bolick *et al.*, 2003; Johnson and Heymach, 2004; Ryan *et al.*, 2004; Mesa, 2006; Costa *et al.*, 2012; Tsuda *et al.*, 2013). There are also a few studies on GGTase inhibitors, such as GGTI-2418 and GGTI-298 (Liu *et al.*, 2018; Karasic *et al.*, 2019). Recently, some potential ICMT inhibitors have also emerged, such as UCM-1336 and C75 (Marín-Ramos *et al.*, 2019; Chen *et al.*, 2021). Finally, recent efforts to find new Rce1 inhibitors have focused on the development of non-peptide-based small molecule compounds. Such compounds are expected to have better cell permeability and be easier to synthesize compared to peptide and natural compound-based inhibitors. However, no effective and specific Rce1 inhibitors have been identified yet (Mohammed *et al.*, 2016; Hampton *et al.*, 2018).

The α4-β6-α5 interface (α4-β6-α5 interface) was found to be important for RAS dimerization or nanocluster formation on the plasma membrane. NS1, a drug that is currently being investigated, binds to the α4-β6-α5 region of RAS, disrupting RAS oligomerization to block its normal function (Spencer-Smith *et al.*, 2017).

The RAS guanylate exchange cycle is mediated by RAS guanine nucleotide exchange factor (RAS GEF) and RAS GTPase activating protein (RAS GAP). RAS GEF catalyzes the conversion of GDP to GTP, turning RAS from an inactive to an active state. RAS GAP activates GTPase, turning the GTP-bound RAS back to GDP-bound RAS (Lito *et al.*, 2016). RAS GEFs include son of sevenless (SOS), Src homology-2-containing protein tyrosine phosphatase 2 (SHP2), RAS guanine nucleotide releasing factor (rasGRF), to name a few. While inhibitors of SOS and SHP2 have been studied more deeply, some inhibitors being currently studied include BAY-293, SHP-099, RMC-4550, etc. (Hillig *et al.*, 2019; Wang *et al.*, 2020a; Song *et al.*, 2021). According to a report, the selective suppression of at least one of the RAS GAPs (RASAL1, DAB2IP, or NF1) results in unrestrained activation of wild-type RAS in human hepatocellular carcinomas (HCC) (Calvisi *et al.*, 2011). A similar situation was found in breast cancer, resulting in the suppression of RASAL2 (Shen *et al.*, 2013). This indicates the potential of targeting RAS GAPs in certain cancers.

Active RAS proteins interact with many downstream effector molecules through RAS binding domains (RBDs). A novel pan-RAS inhibitor called Pen-cRaf-v1 with desirable target specificity has been reported by searching a combinatorial library consisting of RBDs and cell-permeable peptides (CPPs). This provides a promising scaffold for further development of RAS inhibitors (Nomura *et al.*,

2021). In another approach, RAS simulants could bind RBDs, but no downstream effector molecule was activated. For example, Rigosertib, a small molecule RAS simulant, binds to RBDs of multiple RAS effectors and blocked their interaction with RAS proteins (Wang *et al.*, 2019). In summary, *ras* can now be directly or indirectly targeted, as shown in Fig. 1.

Myc inhibitors

Previous studies of *myc* pathway inhibition mainly focused on the transcription, translation, stabilization, and activation of *myc*, as shown in Fig. 2.

A general feature of *myc* dysregulation in tumor cells is that it is transcriptionally enhanced by Super-Enhancers (SEs), implying that inhibition of SEs might suppress *myc* transcription. For example, the inhibition of Cyclin-dependent kinase (CDK) 7 and/or CDK9, which are SEs, was found greatly reduce MYC expression, accompanied by extensive transcriptional downregulation of *myc* target genes. Additionally, CDK7 inhibitors like THZ1 and CDK9 inhibitors like PC585 were found to have potent antitumor effects against MYC in many *myc*-driven cancers (Chen *et al.*, 2018; Thandapani, 2019). Further, CDK9 could also be rapidly degraded induced by a selective CDK9 degrader, THAL-SNS-032, consisting of a CDK-binding SNS-032 ligand linked to a thalidomide derivative that binds the E3 ubiquitin ligase Cereblon (CRBN) (Olson *et al.*, 2018). Bromodomain-containing protein 4 (BRD4) is a member of the bromodomain and extra-terminal domain (BET) family of proteins and is widely recognized for its role in the organization of super-enhancers and the regulation of oncogene expression (Donati *et al.*, 2018). BRD4 could be inhibited by small molecules such as JQ1 and OTX015 (Delmore *et al.*, 2011; Boi *et al.*, 2015), and could be also degraded by PROTACs (Otto *et al.*, 2019). In one study, the novel BET-PROTACs (ARV-825 and ARV-771) that degrade BRD4 were compared with the BET bromodomain inhibitor (BETi) OTX015. At equimolar concentrations, ARV-825 and ARV-771 were more potent than the BETi OTX015 in inducing apoptosis of cultured and primary mantle cell lymphoma (MCL) cells (Sun *et al.*, 2018).

A possible biochemical crosstalk between *myc* and mechanistic target of rapamycin (mTOR) pathways was found in liver cancer. mTORC1 functions by regulating the downstream cascades that are necessary for *c-myc*-induced carcinogenesis (Liu *et al.*, 2017). Interestingly, the pharmacological inhibition of the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway significantly reduced *myc* translational levels and showed significant therapeutic effects in many *myc*-driven cancers (Chen *et al.*, 2018).

Though the stability of MYC is tightly controlled, suppressing Ubiquitin-specific proteases (USPs), Aurora kinases, and Polo-like kinases (PLKs) was found to destabilize MYC and suppress MYC-driven tumors (Chen *et al.*, 2018; Tavana *et al.*, 2016). For example, USP7, known as a regulator of N-MYC function in neuroblastoma could be

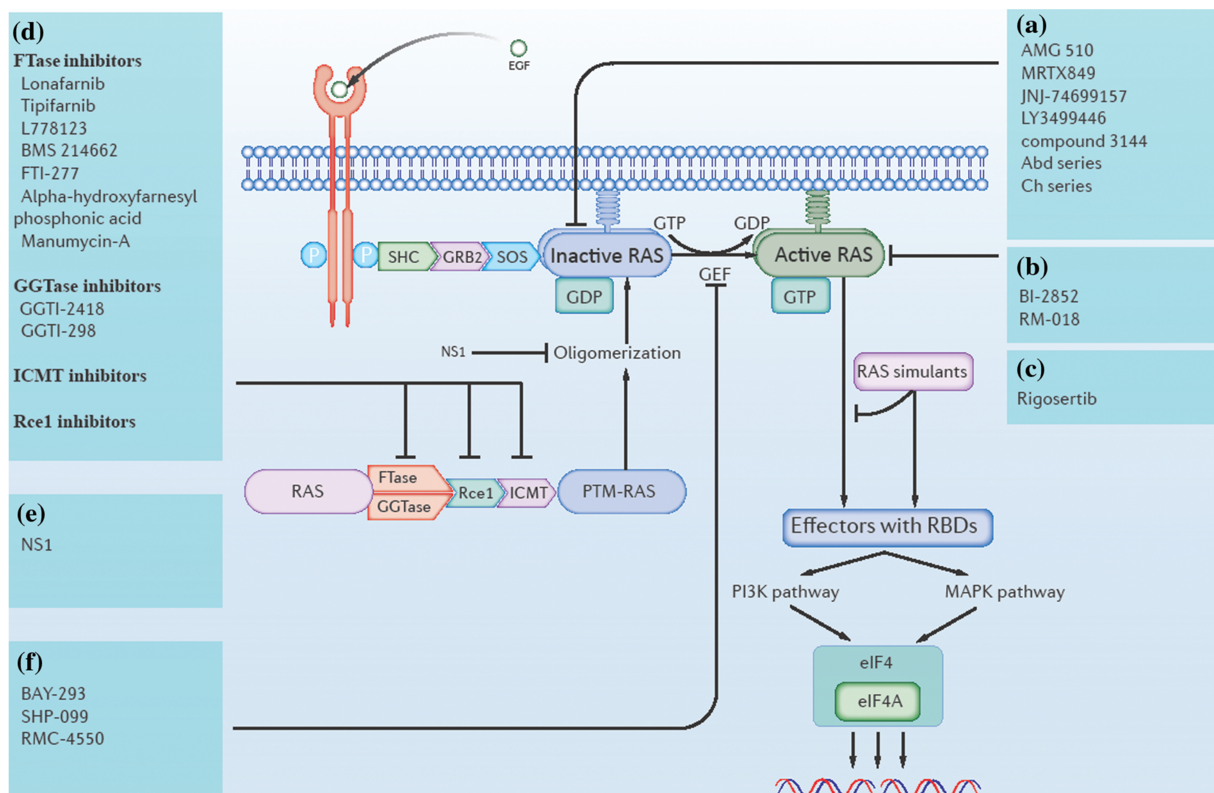

FIGURE 1. Direct and indirect approaches of ras inhibition. (a) Inhibitors that directly target GDP-bound (inactive state) RAS. (b) Inhibitors that directly target GTP-bound (active state) RAS. (c) RAS simulants block downstream RAS activation. (d) RAS post-translational modification (PTM) inhibitors, including farnesyl transferase (FTase) inhibitors, geranylgeranyl transferase (GGTase) inhibitors, isoprenylcysteine carboxyl methyltransferase (ICMT) inhibitors, and RAS-converting enzyme (Rce1) inhibitors. (e) Inhibitors of RAS oligomerization. (f) RAS guanine nucleotide exchange factor (RAS GEF) inhibitors.

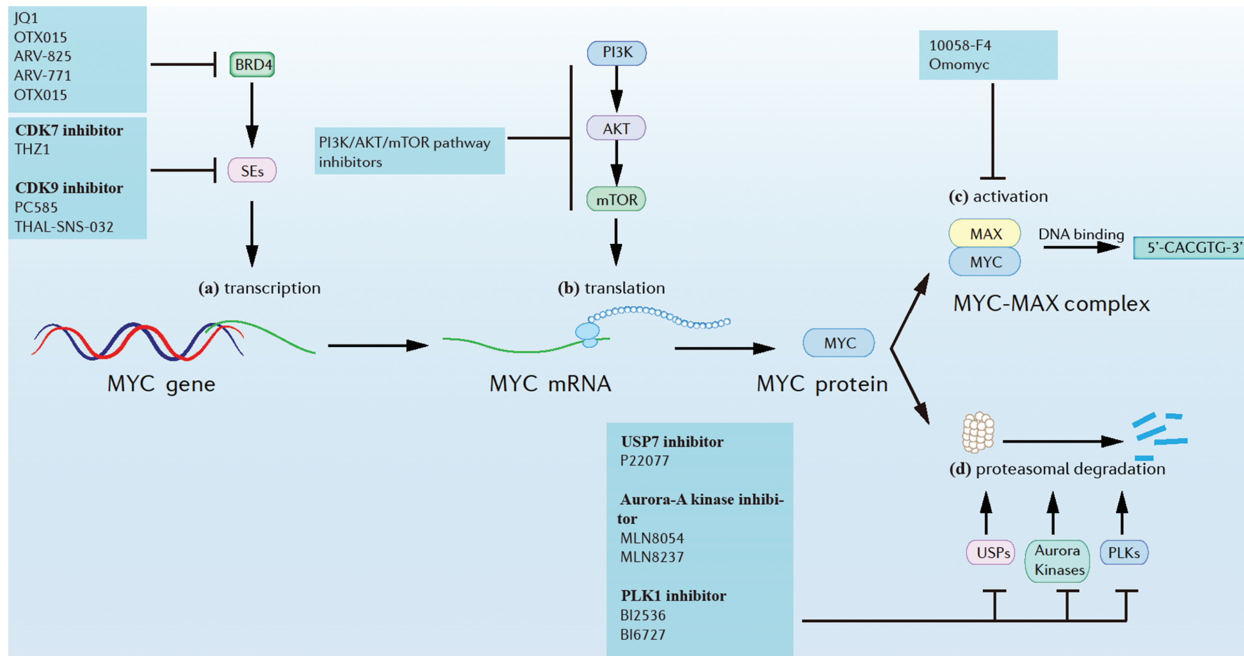

FIGURE 2. Approaches of *myc* inhibition at different levels. (a) *Myc* transcription. (b) *Myc* translation. (c) MYC activation. (d) MYC proteasomal degradation.

suppressed by small molecule inhibitor P22077, which caused tumor suppression (Tavana *et al.*, 2016). Further, aurora-A kinase, a kinase that protects N-MYC from proteasomal degradation, could be inhibited by several small molecules like MLN8054 and MLN8237. This resulted in N-MYC degradation and tumor suppression in neuroblastoma (Brockmann *et al.*, 2013). PLK1, a kinase that forms a positive feedforward activation loop with MYC could be inhibited by inhibitors like BI2536 and BI6727, resulting in the potent apoptosis of *myc*-overexpressing tumor cells (Xiao *et al.*, 2016).

The MYC-MAX complex is required for MYC binding to DNA and subsequent activation of target gene transcription. In one report, the inhibitor 10058-F4 targeted and disrupted the MYC-MAX complex in HL60 cells, while Omomyc preferentially bound MAX over MYC and inhibited MYC-mediated transcription by replacing MYC/MAX heterodimers with Omomyc/max heterodimers (Chen *et al.*, 2018; Demma *et al.*, 2019).

To summarize, substantial progress has been made in the study of targeting *myc* pathways. However, targeting MYC proteins directly still seems to be challenging, since MYC proteins lack appropriate pockets or grooves that can serve as inhibitor binding sites (Wang *et al.*, 2019).

Tp53 inhibitors

On one hand, as the wild-type *tp53* gene is considered one of the tumor suppressor genes, previous studies have focused on preventing *tp53* from losing its function as a tumor suppressor gene. On the other hand, mutant *tp53* genes are considered therapeutic targets as oncogenes. Such previously researched ideas mainly included restoring wild type function of P53 mutants by altering their protein structures, altering the proteasomal degradation of P53 proteins, *tp53* gene editing, and inducing synthetic lethality in *tp53*-mutated cancer cells, as shown in Fig. 3.

To restore the wild-type function of P53 mutants, several attempts have been tried and reported. For example, PRIMA-1 (P53 reactivation and induction of massive apoptosis-1) and its structural analog PRIMA-1Met (APR-246) played a role as cysteine-binding compounds in refolding mutant P53 (Peng *et al.*, 2013). Additionally, compounds like PK7088 bound to a crevice in p.Y220C mutant P53 proteins, increasing the fraction of correctly folded p.Y220C mutant P53 in cells (Liu *et al.*, 2013). Further, compounds like NSC319726 (ZMC1) could reactivate several P53 mutants with impaired zinc binding through their zinc ion-chelating properties (Blanden *et al.*, 2015; Soussi and Wiman, 2015; Bykov *et al.*, 2018).

The inhibition of MDM2 protein, a P53-specific E3 ubiquitin ligase, and (or) MDM4, a protein with structural homology to MDM2 has been explored as potential approaches to block the proteasomal degradation of P53. Several MDM2/4 antagonists can block the degradation of P53 (Duffy *et al.*, 2014). For example, MDM2 antagonists, such as Nutlins could inhibit MDM2-P53 interactions, resulting in the apoptosis of malignant cells (Demicco, 2019). Additionally, efforts have been made in searching for MDM4 antagonists, for example, compounds such as SJ-172550 and XI-006 could inhibit MDM4 effectively (Reed *et al.*, 2010; Pishas *et al.*, 2015). Moreover, several dual MDM2-MDM4 antagonists, such as PMI (TSFAEYWNLLSP) and ATSP-7041 presented a stronger affinity with MDM2 /4 than the affinity between P53 and MDM2/4 (Pazgier *et al.*, 2009; Tiwari and Verma, 2017). However, a possible side effect of treatment with MDM2/4 antagonists is that WT P53 levels may accumulate in normal cells and induce inappropriate apoptosis and cell

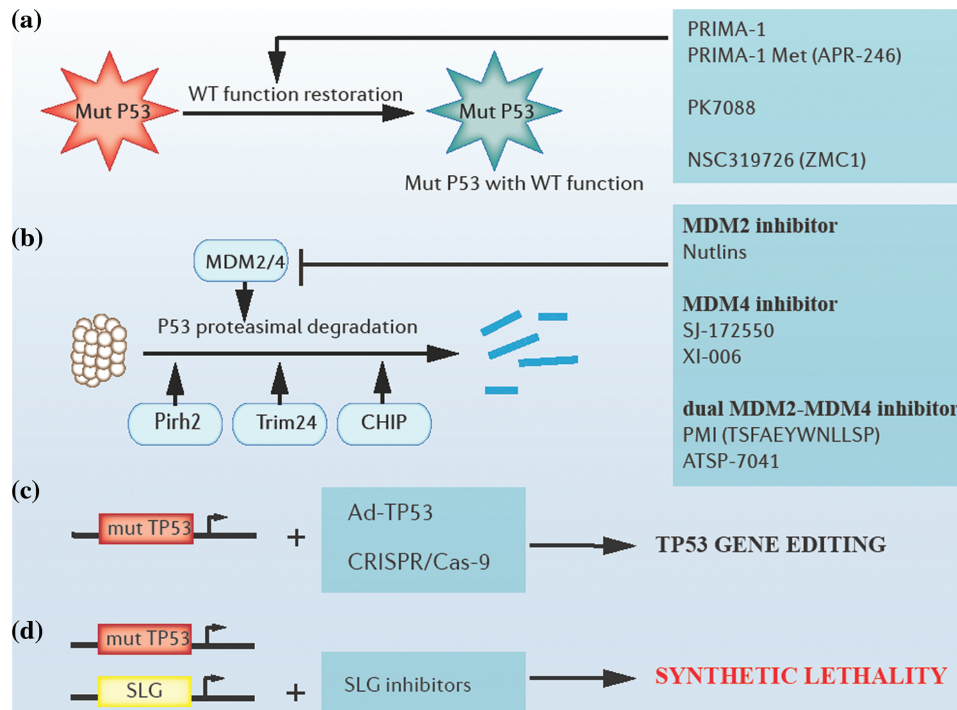

FIGURE 3. Approaches of targeting tp53. (a) Restoring the wild-type function of P53 mutants by altering their protein structures. (b) Blocking proteasomal degradation of P53 by targeting E3 ubiquitin ligases. (c) Tp53 adenoviral vectors and clustered regulatory interspaced short palindromic repeats (CRISPR)/CRISPR-associated system (Cas9)-based gene editing. (d) Synthetic lethality-based p53 targeting. Mut P53: mutant P53 proteins; WT: wild type; mut TP53: mutant tp53 genes; Ad-TP53: tp53 adenoviral vectors; SLG: synthetic lethality gene.

death, which refrains us from jumping to optimistic conclusions (Duffy *et al.*, 2014). Apart from MDM2, many other ubiquitin ligases that participate in the degradation of P53 have been identified recently, including Pirh2, Trim24, Carboxyl terminus of HSP70-interacting protein (CHIP), etc. (Jain and Barton, 2009; Wang *et al.*, 2011; Soussi and Wiman, 2015; Wang *et al.*, 2020b).

Tp53 gene therapy is also a current hot topic. Firstly, efficacy in *tp53* gene replacement employing some viral vectors like *tp53* adenoviral vectors was reported in prostate cancer in clinical trials (Tamura *et al.*, 2018). Secondly, clustered regulatory interspaced short palindromic repeats (CRISPR)/ CRISPR-associated system (Cas9)-mediated genome editing has a prospect in editing the *tp53* gene, and relevant tests are in progress (Mirgayazova *et al.*, 2020).

Moreover, an interesting concept has recently achieved brilliant clinical success, that is, synthetic lethality. This includes mutations in genes that lead to cell or organism death when occurring in combination with mutations in one or more other genes. One of the most classic examples is that of tumors lacking DNA repair function due to the loss of expression of functional breast cancer 1 (BRCA1) or breast cancer 2 (BRCA2) proteins that are extremely sensitive to poly (ADP-ribose) polymerase (PARP) enzyme inhibition (Farmer *et al.*, 2005). Similar mechanisms can be applied to the targeting of *tp53*, and valuable progress has been made in the synthetic lethality between the *tp53* gene and ataxia telangiectasia and Rad3-related protein (ATR)/ Chk1, ataxia telangiectasia mutated (ATM)/Chk2 or p38/ MAPK-activated protein kinase 2 (MK2), and other signaling pathways (Kawasumi *et al.*, 2014; Morandell and Yaffe, 2012; Pabla *et al.*, 2008).

Emerging Research Ideas for Targeting the "Undruggable" Cancer Driver Genes

PROTACs technology

Protein-protein interaction (PPI) interfaces may be large and flat between "undruggable" proteins and other proteins, which makes it tricky to design drugs against them. However, a question comes as to whether we use the PPIs of the human body to help us target these proteins. In the process of protein degradation, E3 ubiquitin ligase specifically recognizes the substrate through PPI, which allows ubiquitin transfer to the substrate protein and directs the substrate to degrade at the proteasome. PROTACs technology aims to develop a linker molecule that binds to the E3 ubiquitin ligase and the target protein, simultaneously, promoting the ubiquitination and subsequent hydrolysis of the target protein, as shown in Fig. 4. Since PROTACs work with E3 ubiquitin ligases, they only need to bind briefly and loosely to the target protein without continuously occupying the active site of the target protein to block the function (Neklesa *et al.*, 2017; Schapira *et al.*, 2019).

The potential of PROTACs in tackling the "undruggable" molecules was shown in some experiments, as shown in Table 1. For example, K-RAS-G12C could be degraded ubiquitously *in vitro* by PROTACs, whereas endogenous H/ K-RAS proteins could be degraded by the affinity-directed protein missile (AdPROM) system (Röth *et al.*, 2020; Simpson *et al.*, 2020; Zeng *et al.*, 2020). As for transcription factors, especially nuclear receptors (NRs), which are traditionally considered "undruggable", the application of PROTACs technology has progressed significantly. For example, ARCC-4, a low-nanomolar androgen receptor

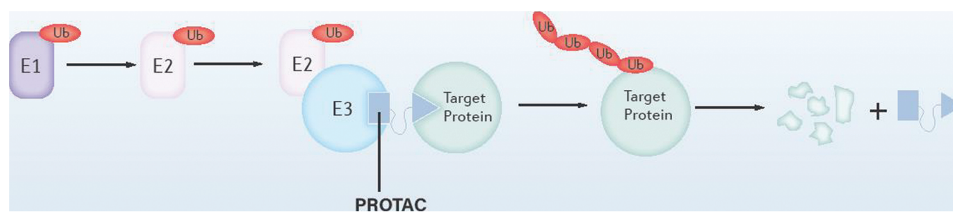

FIGURE 4. Schematic diagram of the structure of the proteolysis targeting chimera (PROTAC) system. As illustrated, PROTAC binds to both E3 ubiquitin ligase and the target proteins, which promotes the ubiquitination and degradation of the target proteins.

PROTAC derivative could degrade cellular androgen receptors (Salami *et al.*, 2018; Flanagan and Neklesa, 2019). Additionally, indirect ubiquitination and degradation of transcriptional regulator BRD4 could be induced by the novel BET-PROTACs like ARV-825 and ARV-771 to cause MYC inhibition and antitumor activity in a few cancer cell lines including colorectal cancer (CRC) cells (Sun *et al.*, 2018; Otto *et al.*, 2019). Further, selective degradation of CDK9 could also be induced by PROTAC molecules like THAL-SNS-032 (Olson *et al.*, 2018). Downstream of the RAS pathway, mutants of BRAF (V600E), MEK1/2, could be ubiquitinated and degraded by PROTACs (Posternak *et al.*, 2020; Wang *et al.*, 2021). PDEδ (PDE6 delta subunit) has a role in promoting the diffusion and proper localization of RAS proteins on the cell membrane. The normal function of RAS proteins was inhibited by ubiquitination and degradation by the PROTACs technology (Jiang *et al.*, 2017; Cheng *et al.*, 2020). It is also possible to indirectly inhibit RAS by degrading SHP2 using PROTACs (Yang *et al.*, 2021). Several PROTACs have been developed to target the degradation of EGFR (Zheng and Tao, 2020), which could indirectly inhibit downstream pathways such as RAS and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. For targeting *TP53*,

TABLE 1

Applications of proteolysis targeting chimeras (PROTACs) on targeting targets that are related to "undruggable" oncogenes and tumor suppressor genes. Types of E3 ubiquitin ligases bound by each PROTAC, target proteins of each PROTAC, and reported characteristics of each PROTAC are presented below

PROTACs	E3 ligase	Target	Characteristics reported	References
Compound 13 (XY-4-88)	CRBN	KRAS-G12C	*In vitro*	Zeng *et al.* (2020)
AdPROM	VHL	H/KRAS	Endogenous	Röth *et al.* (2020)
ARCC-4	VHL	Androgen receptor (AR)	Inhibits prostate tumor cell proliferation	Salami *et al.* (2018)
ARV-825	CRBN	BRD4	Demonstrates a unique therapeutic strategy in which targeting BRD4 for degradation leads to sustained inhibition of oncogenic *myc* expression for effective treatment of pancreatic cancer	Minko (2020)
ARV-771	VHL	BRD4	Demonstrates dramatically improved efficacy in cellular models of castration-resistant prostate cancer (CRPC) as compared with BET inhibition	Raina *et al.* (2016)
THAL-SNS-032	CRBN	CDK9	An attractive target for cancers that exhibit aberrant transcription, especially those driven by proto-oncogenes such as *c-myc*	Olson *et al.* (2018)
P4B	CRBN	BRAF (V600E)	RAS downstream	Posternak *et al.* (2020)
Compound 1 (Wei *et al.*, 2019), compound2 (Vollmer *et al.*, 2020), compound3 (Hu *et al.*, 2020)	VHL	MEK1/2	RAS downstream	Wang *et al.* (2021)
Compound 17f	CRBN	PDEδ	Demonstrates significantly improved antiproliferative potency in *k-ras* mutated SW480 cells	Cheng *et al.* (2020)
11(ZB-S-29)	CRBN	SHP2	Indirectly inhibits RAS	Yang *et al.* (2021)
MS39/PROTAC3	VHL	EGFR	RAS upstream	Zheng and Tao (2020)
MS154	CRBN	EGFR		
MD-224	CRBN	MDM2	Blocks the P53 degradation	Fang *et al.* (2020)

MDM2 could be degraded by PROTACs technology, which inhibited the degradation of P53 by MDM2 and activated P53 (Fang *et al.*, 2020; Demir *et al.*, 2021).

Immunotherapy

Immunotherapy plays a critical role in cancer treatment in recent years. Many such novel methods may be effective in overcoming undruggable targets. In the following section, bispecific antibodies and cancer vaccines are mainly introduced.

Bispecific antibodies (bsAb) are antibodies that specifically target two antigens at the same time. Here is an example to illustrate the principle. Recently, a bispecific antibody was reported that targets the neoantigen R175H generated by *tp53* mutation on the one hand and the T cell receptor (TCR) on the other hand, causing T cells to release cytotoxic proteins that kill tumor cells (Hsiue *et al.*, 2021). In theory, this approach would only bind T cells to the vicinity of tumor cells. It was thus demonstrated that T cells could be effectively activated by such bispecific antibodies to kill tumor cells despite the low antigen density on their surface. Theoretically, this approach could be used to treat cancers containing other mutations that are difficult to target by conventional means.

Cancer vaccines induce and amplify antigen-specific immune responses and have long been considered potentially valuable tools for the treatment of cancer. Protein cancer vaccines and mRNA cancer vaccines are discussed herewith. Protein cancer vaccines are based on the principle of activating dendritic cells and triggering T-cell responses to target proteins by injecting them with target proteins and some cytokines. Examples include the intradermal injection of mutated RAS protein peptides and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Moore *et al.*, 2020). In contrast to protein cancer vaccines, mRNA vaccines are based on the principle of injecting lipid-soluble nanoparticles containing the target protein mRNA. The mRNA nanoparticles are then taken up by antigen-presenting cells, translated into proteins, and presented to the cell surface, which triggers the T-cell response to the target protein. Examples include the intramuscular injection of mRNA nanoparticles containing mRNAs encoding common K-RAS mutations (G12C, G12D, G12V, and G13D) elicited T-cell responses (Moore *et al.*, 2020). Overall, cancer vaccines are a smart alternative for the genes that are difficult to target by conventional approaches.

Artificial intelligence

Although tremendous effort has been made on such "undruggable" molecules, little progress has been made yet. However, graphics processing unit (GPU) computing and deep learning now accelerate drug discovery, including the discovery of drugs targeting these "undruggable" molecules. Procedures like molecular dynamics simulations and protein structure determination can be accelerated with the help of deep learning models and GPU parallel computing (Pandey *et al.*, 2022). Traditionally, evaluating the druggability of potential targets requires considerable time and financial cost in the analysis of three-dimensional (3D) protein structures. However, the situation is about to change thanks to the development of network-based and machine learning (ML)-based artificial intelligence algorithms (You *et al.*, 2022).

The application prospects of AI in the pocket druggability prediction are promising. For example, PockDrug-Server is a web server based on the protein-protein interaction network for pocket druggability prediction, which presents efficiency in both estimated pockets guided by the ligand proximity or solely based on protein structure information (Hussein *et al.*, 2015). Since approaches like PockDrug heavily depend on accurate 3D protein structures, recent ML-based AI algorithms which can predict the 3D structure of a protein from its genetic sequence could be very helpful. Another example is AlphaFold2, one of the state-of-the-art machine learning methods developed by the DeepMind company in 2021. It is claimed to be able to predict structures of almost the entire human proteome (Tunyasuvunakool *et al.*, 2021). Moreover, other protein structure-predicting ML methods like the trRosetta algorithm also showed promising potential in the accurate prediction of protein structure (Yang *et al.*, 2020).

In addition to pocket druggability prediction, the prediction of interactions between drug and target or drug and the drug is critical for new drug discovery. For processes like drug screening and drug repurposing, network-based and ML-based artificial intelligence algorithms can be employed as powerful tools (You *et al.*, 2022). AI-based drug-target interactions (DTIs) predictions are mainly divided into 2 categories, one is "top-down", which starts from observable characteristics to predict the interaction, whereas the other is "bottom-up", which starts from molecular features to predict interactions (You *et al.*, 2022).

Last but not least, AI is also widely used in the prediction of drug properties, comprising ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction and predicting properties applied in clinical trials for seeking optimal treatment plans (You *et al.*, 2022).

More specifically, artificial intelligence can be employed as the right helper to accelerate the development of some aforementioned emerging approaches of targeting "undruggable" molecules. Several computational modeling tools are now available to accelerate PROTAC design, which may minimize the spending cost and time (Drummond and Williams, 2019; Drummond *et al.*, 2020). As with cancer immunotherapies, similar advantages of AI are demonstrated in this regard. With the use of high-throughput sequencing data, several *in silico* methods or tools which facilitate the identification of tumor neoantigens may accelerate the development of cancer immunotherapies (Zhou *et al.*, 2019). Preclinical trials of cancer immunotherapies like chimeric antigen receptor (CAR)–T cell therapy and cancer vaccines can be reduced by applying mathematical models *in silico* (Barros *et al.*, 2021; Lőrincz *et al.*, 2021; Valle *et al.*, 2021).

In summary, we consider that with the development of AI, an increasing number of AI-based applications like potential target druggability prediction, new drug discovery, and the prediction of drug properties would provide better help in developing potent drugs, including those targeting

currently "undruggable" molecules. With the application of AI, it may be easier for scientific workers to remove the barriers when developing drugs for those targets that are presently "undruggable".

The Possible Challenges of Targeting the "Undruggable" Cancer Driver Genes

The possible challenges of targeting the "undruggable" oncogenes and tumor suppressor genes can be mainly summarized in three parts, that is, technical challenges, financial challenges, and ideological challenges.

Firstly, in addition to the difficulties of targeting summarized in the introduction section, toxicity could be another challenge for targeting the "undruggable" molecules. This is mainly because most of the "undruggable" oncogenes and tumor suppressor genes, including *ras*, *myc*, and *tp53*, all play crucial roles in normal cells (Simanshu *et al.*, 2017; Levine, 2020; Duffy *et al.*, 2021). Further, drug resistance is a great challenge besides effectiveness and toxicity. For example, resistance to some KRAS-G12C inhibitors could be caused by the increased level of RAS dimerization or the GTP-bound RAS proteins (Moore *et al.*, 2020). Tumor cells can suppress or evade the immune system by expressing several immune checkpoints, leading to downregulation of the immune response in human cancer and hindrance to immunotherapy. Elevated levels of immune checkpoints like programmed cell death protein ligand 1 (PDL1) in NSCLC tumors with *k-ras* mutations and increased cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression in liver cancer tumors with *tp53* mutations can be an obstacle to applying immunotherapy to the "undruggable" oncogenes and tumor suppressor genes (Ninomiya and Hotta, 2018; Long *et al.*, 2019).

Secondly, the investment in this research with technical challenges is high and risky at the moment. Therefore, persuading stakeholder commitment to resources to invest may be a challenge as big as technical challenges. Thirdly, we need to break away from dogmatism and avoid conventional thinking. Targeting these "undruggable" molecules has been done for many years, but the current progress is few, so we need to reflect on what is wrong with our current research methods and ideas, and how to improve them.

To summarize, how to overcome these challenges is the current question we need to think about.

Conclusion

While direct targeting of "undruggable" molecules has always been the goal of the research, indirect targeting is a temporary alternative measure. *Ras* is a critical oncogene in cancer development and its associated proteins are now gradually becoming directly targetable by several RAS inhibitors represented by Sotorasib. MYC and P53 proteins encoded by *myc* and *tp53*, however, are both unable to be currently directly targeted, but several alternative approaches have documented results in indirectly targeting them. In the quest to target "undruggable" molecules, some emerging approaches like PROTACs, bispecific antibodies, and cancer vaccines all have great potential. In addition, AI can play a significant role in accelerating drug discovery. This article has summarized the conventional and some novel approaches that target *ras*, *myc*, *tp53*, and a few other molecules that are considered "undruggable". This contributes to our understanding of the current status of targeted anti-cancer drug development. Looking ahead, there are challenges not only from drug effectiveness, toxicity, and drug resistance but also challenges from economical and ideological aspects. The ways in which we can tackle those barriers is the question raised by this article. Drug discovery of the "undruggable" molecules previously seemed to be an impossible mission, but now with the rapid development of technology, this would be a fruitful area for future work.

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