

## REVIEW

# Protein tyrosine phosphatases: emerging role in cancer therapy resistance

Min Zhao<sup>1</sup> | Wen Shuai<sup>1</sup> | Zehao Su<sup>1,2</sup> | Ping Xu<sup>3</sup> | Aoxue Wang<sup>1</sup> | Qiu Sun<sup>1</sup> | Guan Wang<sup>1</sup> 

<sup>1</sup>Innovation Center of Nursing Research, Nursing Key Laboratory of Sichuan Province, Department of Biotherapy, Cancer Center and State Key Laboratory of Biotherapy, National Clinical Research Center for Geriatrics, West China Hospital, West China School of Nursing, Sichuan University, Chengdu, Sichuan, P. R. China

<sup>2</sup>West China Biomedical Big Data Center, Med-X Center for Informatics, Sichuan University, Chengdu, Sichuan, P. R. China

<sup>3</sup>Emergency Department, Zigong Fourth People's Hospital, Chengdu, Sichuan, P. R. China

## Correspondence

Guan Wang and Qiu Sun, Innovation Center of Nursing Research, Nursing Key Laboratory of Sichuan Province, Department of Biotherapy, Cancer Center and State Key Laboratory of Biotherapy, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University/West China School of Nursing, Sichuan University, Chengdu 610041, Sichuan, P. R. China.

## Abstract

**Background:** Tyrosine phosphorylation of intracellular proteins is a post-translational modification that plays a regulatory role in signal transduction during cellular events. Dephosphorylation of signal transduction proteins caused by protein tyrosine phosphatases (PTPs) contributed their role as a convergent node to mediate cross-talk between signaling pathways. In the context of cancer, PTP-mediated pathways have been identified as signaling hubs that enabled cancer cells to mitigate stress induced by clinical therapy. This is achieved by the promotion of constitutive activation of growth-stimulatory

**List of abbreviations:** ALK, anaplastic lymphoma kinase; AKT, protein kinase B; AP-1, activator protein-1; BRAF, V-raf murine sarcoma viral oncogene homolog B1; BRCA, breast cancer susceptibility gene; CAR-T, chimeric antigen receptor T-cell immunotherapy; CDK4/6, cyclin-dependent kinase 4/6; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T lymphocyte associate protein-4; CSF1, colony-stimulating factor-1; CSF1R, colony-stimulating factor-1 receptor; CRISPR, clustered regularly interspaced palindromic repeats; DCR, disease control rate; DLT, dose limiting toxicity; DUSP4, dual-specificity phosphatase 4; DUSP6, dual-specificity phosphatase 6; EGFR, epidermal growth factor receptor; EMT6, experimental mammary tumour-6; ERK, extracellular regulated protein kinase; Gab2, Grb2-associated-binding protein 2; GDP, guanosine diphosphate; Grb2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; HCC, hepatocellular carcinoma; IFN- $\gamma$ , interferon  $\gamma$ ; IFNGR, interferon- $\gamma$  receptor; IL-6, interleukin-6; IRF, interferon regulatory factor; ITIM, immune receptor tyrosine-based inhibitory motif; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; KRAS, kirsten rat sarcoma virus; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; MHC-I, major histocompatibility complex class I; MKP2/3, mitogen-activated protein kinase phosphatases 2/3; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-cells; NF- $\kappa$ B, nuclear factor kappa-B; NRAS, neuroblastoma RAS viral oncogene homolog; NSCLC, non-small cell lung cancer; ORR, objective response rate; PARP, poly-ADP ribose polymerase; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PTP, protein tyrosine phosphatase; PTPN2, protein tyrosine phosphatase non-receptor 2; PTPN11, protein tyrosine phosphatase non-receptor 11; QD, quaque die; RAS, rat sarcoma virus; RasGAP, RAS GTPase-activating protein; RAF, Raf protein kinase; RIPR, receptor inhibition by phosphatase recruitment; RNA-seq, RNA-sequencing; SCC, squamous cell carcinoma; SHP2, src homology-2 domain-containing phosphatase 2; Slamf6<sup>+</sup>, signaling lymphocytic activation molecule family member 6-positive; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TC-PTP, T cell protein tyrosine phosphatase; TCR, T cell receptor; Tim-3<sup>+</sup>, T cell immunoglobulin domain and mucin domain-3-positive; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TRAE, treatment-related adverse event; WT, wild type.

Min Zhao, Wen Shuai, and Zehao Su contributed equally to this work.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Cancer Communications* published by John Wiley & Sons Australia, Ltd on behalf of Sun Yat-sen University Cancer Center.

Email: [guan8079@163.com](mailto:guan8079@163.com) and  
[sunqiu@scu.edu.cn](mailto:sunqiu@scu.edu.cn)

### Funding information

National Natural Science Foundation of China, Grant/Award Numbers: 82273770, 22177083; Natural Science Foundation of Sichuan Province, Grant/Award Number: 2022NSFSC1290; 135 Project for Disciplines of Excellence–Clinical Research Incubation Project; West China Hospital; West China Nursing Discipline Development Special Fund Project; Sichuan University, Grant/Award Numbers: ZYJC21016, HXHL21011

signaling pathways or modulation of the immune-suppressive tumor microenvironment. Preclinical evidences suggested that anticancer drugs will release their greatest therapeutic potency when combined with PTP inhibitors, reversing drug resistance that was responsible for clinical failures during cancer therapy.

**Areas covered:** This review aimed to elaborate recent insights that supported the involvement of PTP-mediated pathways in the development of resistance to targeted therapy and immune-checkpoint therapy.

**Expert opinion:** This review proposed the notion of PTP inhibition in anti-cancer combination therapy as a potential strategy in clinic to achieve long-term tumor regression. Ongoing clinical trials are currently underway to assess the safety and efficacy of combination therapy in advanced-stage tumors.

### KEYWORDS

cancer treatment, combination therapy, drug resistance, protein tyrosine phosphatase

## 1 | BACKGROUND

The homeostasis of protein tyrosine phosphorylation is regarded as an important mechanism for the maintenance of intracellular signal transduction. Recruitment of protein tyrosine phosphatases (PTPs) acts as a prerequisite in the process of dephosphorylation of signal transduction proteins, which underlay the broad participation of PTPs in a diverse array of signaling pathways [1–3]. It is now well-known that some PTPs function in a positive manner downstream of growth-stimulatory and immune-suppressive signaling pathways, thereby regulating the duration and amplitude of cell proliferation and immune tolerance [4, 5]. Under the given circumstances, malfunction of PTPs seemed to be oncogenic to support tumorigenesis in different types of human cancer, ranging from hematological malignancy to solid tumors [6]. This malfunction was observed in two distinct forms: genetic mutations of PTPs during tumorigenesis and feedback activation of PTPs following cancer therapy, leading to the emergence of drug resistance [7, 8]. The past decades have witnessed progress in the discovery of pro-tumorigenic PTPs under the genetic context of specific driver mutations. Notably, Src homology-2 domain-containing phosphatase 2 (SHP2) was the firstly identified oncogenic phosphatase in the PTP family [9, 10]. Less insights were concentrated on the feedback regulation of PTPs in resistance to cancer therapy.

Recent studies have identified that PTP-mediated pathways accounted for one of the possible mechanisms of resistance to targeted therapy and immune checkpoint

therapy. In the context of non-small cell lung cancer (NSCLC) cells resistant to sotorasib (Kirsten rat sarcoma virus with G12C mutation [KRAS<sup>G12C</sup>] inhibitor), a in vivo clustered regularly interspaced palindromic repeats (CRISPR)-Cas9 screening unveiled the presence of sustained proliferative signaling in a SHP2-dependent manner [11]. Additionally, preclinical loss-of-function screening in melanoma mice treated with anti-programmed cell death protein 1 (PD-1) antibody identified that deletion of protein tyrosine phosphatase non-receptor 2 (PTPN2) rendered susceptibility to immune-checkpoint therapy through transcriptional activation of interferon  $\gamma$  (IFN- $\gamma$ ) response genes [2]. These evidences indicated that perturbation of PTPs served as a central signaling hub to buffer stress following cancer therapy. It occurred through promoting constitutive activation of growth-stimulatory signaling pathways or influencing over the immune-suppressive tumor microenvironment. Therefore, targeting PTP inhibition in anticancer combination therapy was probably a potential strategy to overcome clinical resistance and unleash full potential of anticancer agents. Hence, this review focused on the molecular mechanism of PTPs in resistance to targeted therapy and immune-checkpoint therapy. It aimed to highlight the potential role of PTPs as drug-resistant targets in frontline adjuvant therapy. Then, this review provided an overview of the current state of PTP inhibition-based combination regimens in clinical trials, presenting the existent obstacles as well as possible solutions. This review ultimately proposed a prominent strategy of targeting PTP inhibition in anti-cancer therapy to overcome the long-standing conundrum of drug resistance.

## 2 | PTPs MEDIATE RESISTANCE TO TARGETED THERAPY

### 2.1 | Feedback activation of SHP2 in resistance to cancer therapy targeting KRAS mutant

Under physiological condition, SHP2 (encoded by protein tyrosine phosphatase non-receptor 11 [*PTPN11*]) functioned in a scaffolding- or phosphatase-dependent manner to promote the transition of inactive guanosine diphosphate (GDP)-bound KRAS into active guanosine triphosphate (GTP)-bound KRAS [12]. It then triggered downstream cascade activation of the mitogen-activated protein kinase (MAPK) pathway [13]. Genetic mutations in *KRAS* disrupted the guanine exchange cycle, typically by locking *KRAS* in the persistently activated GTP-bound state [14], thereby providing growth advantage for MAPK pathway-driven cancers [15]. In a preclinical model of pancreatic ductal adenocarcinoma (PDAC) with mutated *KRAS*, gene set enrichment analysis revealed that deletion of *PTPN11* induced a clear loss of *KRAS* signaling signature, including downstream mitogen-activated extracellular signal-regulated kinase (MEK), protein kinase B (AKT), and interleukin-6 (IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling [16, 17]. These results indicated that mutant *KRAS* still depended on SHP2 for signal intensification and downstream cascade activation.

Feedback activation of SHP2 following inhibition of the rat sarcoma virus (RAS)-Raf protein kinase (RAF)-MEK pathway conferred to therapeutic resistance in *KRAS* mutant-driven cancers (Figure 1A). In preclinical models of pancreatic and lung cancers harboring mutant *KRAS*, treatment with MEK inhibitors (selumetinib or trametinib) induced a chronic activation of extracellular regulated protein kinases (ERK) over time, leading to a transient delay in tumor growth [16]. Ruess *et al.* [16] observed a significant increase in phosphorylation level and phosphatase activity of SHP2 in resistant pancreatic cancer cells, suggesting a SHP2-dependent positive-feedback loop for amplification of *KRAS* activity to compromise MEK inhibition. Scientists also claimed that combination therapy of trametinib and SHP-099 (SHP2 inhibitor) benefited to impeding ERK reactivation in response to MEK inhibition, resulting in sustained growth inhibition in *KRAS*-mutated PDAC [18]. In clinic, gain-of-function mutation of *KRAS*<sup>G12C</sup> was a well-known driver mutation that accounted for the pathogenesis in 13% of NSCLC [19]. A phase II clinical trial of sotorasib (a *KRAS*<sup>G12C</sup> inhibitor) observed objective response in 37.1% of patients with NSCLC, whereas others bypassed inhibition to resume

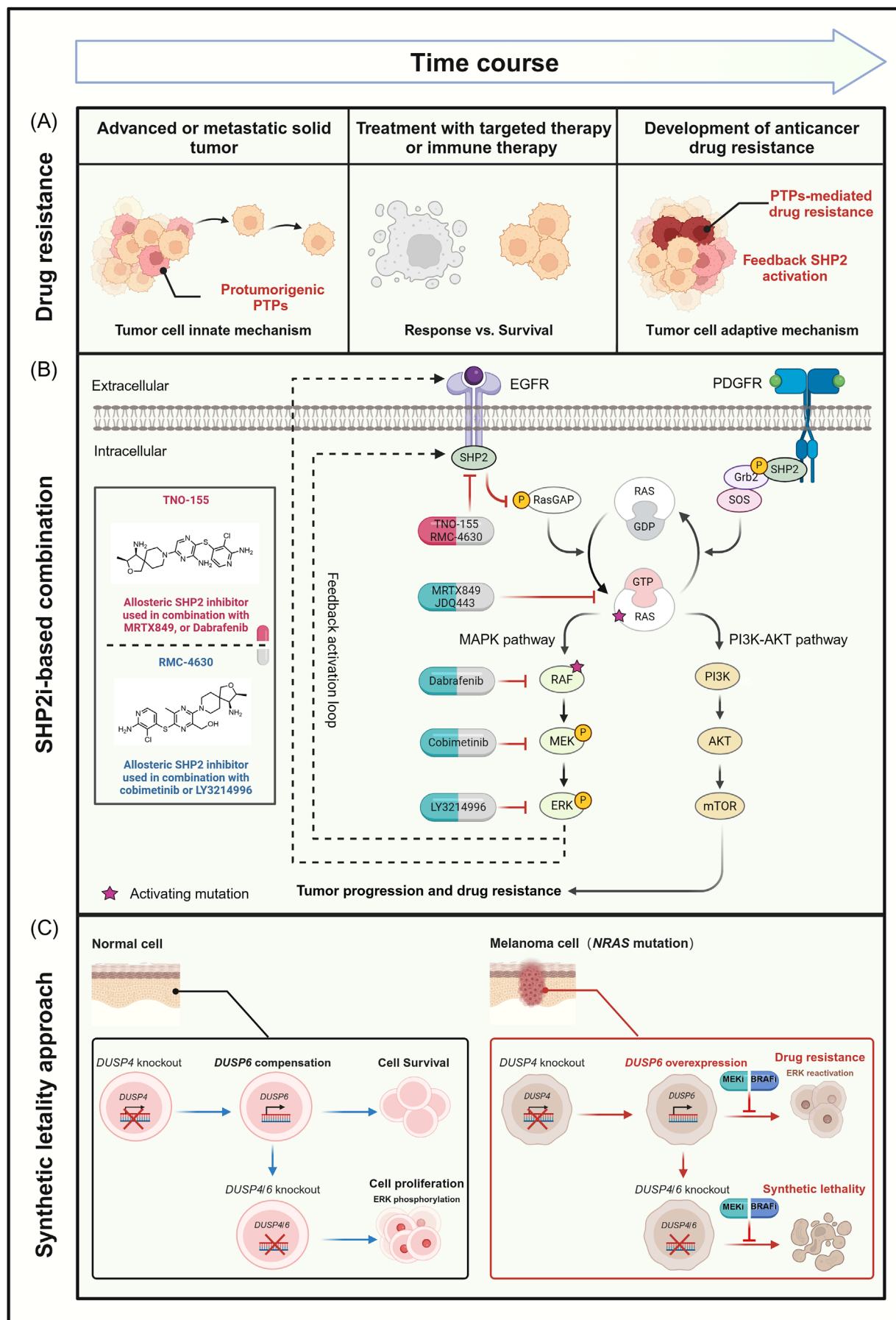
proliferation (NCT03600883) [20, 21]. To identify the candidate genes mediating drug resistance, Xue *et al.* [11] conducted a genome-wide CRISPR-Cas9 screen in NSCLC cells and discovered sustained proliferative signaling in an epidermal growth factor receptor (EGFR)- and SHP2-dependent manner. These results restated the feedback regulation loop of SHP2 in the adaptive reactivation of *KRAS* signaling. Co-targeting SHP2 (RMC-4630) and *KRAS*<sup>G12C</sup> (sotorasib) has been observed to attenuate the onset of drug-induced resistance, and significantly enhanced the antiproliferative effect in lung cancer cells [13] (Figure 1B).

The dependence of *KRAS* on SHP2 phosphatase for full activation underlay the molecular mechanism of drug-induced resistance [16]. These findings manifested that in clinical settings, mutation-specific inhibitors of *KRAS*<sup>G12C</sup> would be most effective when combined with SHP2 inhibitors to achieve sustained tumor regression. Currently, clinical trials of such combination regimen have observed objective response in *KRAS*<sup>G12C</sup>-mutated solid tumors [22, 23].

### 2.2 | Synthetic lethality of dual-specificity phosphatase 4 (*DUSP4*) and dual-specificity phosphatase 6 (*DUSP6*) in MAPK pathway resistant cancer

Synthetic lethality pioneered the next generation of cancer therapeutics for tackling targets that were not classically “druggable” [24]. It referred to recessive lethality under a combination of mutations in two or more separate genes, while inactivation of only one of these genes had little effect on cell viability [25]. The recent success of poly-ADP ribose polymerase (PARP) inhibitors in breast cancer susceptibility gene (*BRCA*)-mutated ovarian cancer was the first clinical trial to apply synthetic lethality to cancer therapy [26]. In the treatment of cancer, synthetically lethal pairs were dependent on the genetic context, namely driver mutations in cancer cells. This approach not only favored a selective cell-killing effect on cancer cells but also spared normal cells due to a lack of fixed genetic alteration, thereby providing a clinical advantage over traditional chemotherapy [27]. Therefore, identification of synthetic lethal pairs benefited the discovery of drug-sensitive targets under the genetic context of driver mutations, thus addressing the issue of treatment resistance to anticancer agents [28].

*DUSP4/6*, encoding MAPK phosphatases 2/3 (MKP2/3), were negative feedback regulators of the MAPK pathway through dephosphorylation of ERK, p38, and C-Jun N-terminal kinase (JNK) [29, 30]. Interestingly, Ito *et al.* [31]





developed a CRISPR paralog targeting library screen and uncovered a novel synthetic lethal interaction between *DUSP4/6* and oncogenic neuroblastoma RAS viral oncogene homolog (*NRAS*) in melanoma cells. Dual knockout of *DUSP4* and *DUSP6* selectively impaired growth of *NRAS*-mutated melanoma cells, in contrast to cell survival when it occurred to wild type (WT) cells or single knockout of *DUSP4* or *DUSP6*. Indeed, 155 clinical specimens from The Cancer Genome Atlas suggested that melanoma tumors harboring oncogenic *NRAS* mutation showed increased expression of *DUSP4/6* than that of WT tumors. These findings indicated that the synthetic lethal effect of *DUSP4/6* was dependent on the genetic context of *NRAS* mutation. Besides, ERK, a shared substrate of *DUSP4/6*, engaged in the resistance of cancer cells with pre-existing oncogenic mutations in the MAPK pathway [32, 33]. Ito *et al.* [31] further discovered that double knockout of *DUSP4/6* led to enhanced phosphorylation of ERK. Pharmacological inhibition of ERK with SCH772984 reduced the growth perturbation upon double knockout of *DUSP4/6*, such that resistant cells characterized as ERK reactivation provided genetic context vulnerable to *DUSP4/6* knockout (Figure 1C). Notably, A375 melanoma cells resistant to dabrafenib became cross-sensitized to *DUSP4/6* inhibition. Then it provided the opportunity to reduce drug resistance through intermittent cyclical drug treatment altering between V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors and *DUSP4/6* inhibition.

In conclusion, the compensatory relationship between functionally redundant genes, *DUSP4* and *DUSP6*, masked their potential to be therapeutic targets in single-gene perturbation screens. The CRISPR paralog targeting library screens uncovered double knockout of *DUSP4/6* as an alternative strategy in *NRAS*-mutated melanoma resistant to therapeutics targeting the MAPK pathway [31]. Small-molecule inhibitors targeting *DUSP4/6* are deficient in current clinical settings, and further efforts in drug discovery would substantiate the synthetic lethal effect of dual inhibition of *DUSP4/6* and *NRAS* in drug-resistant melanoma.

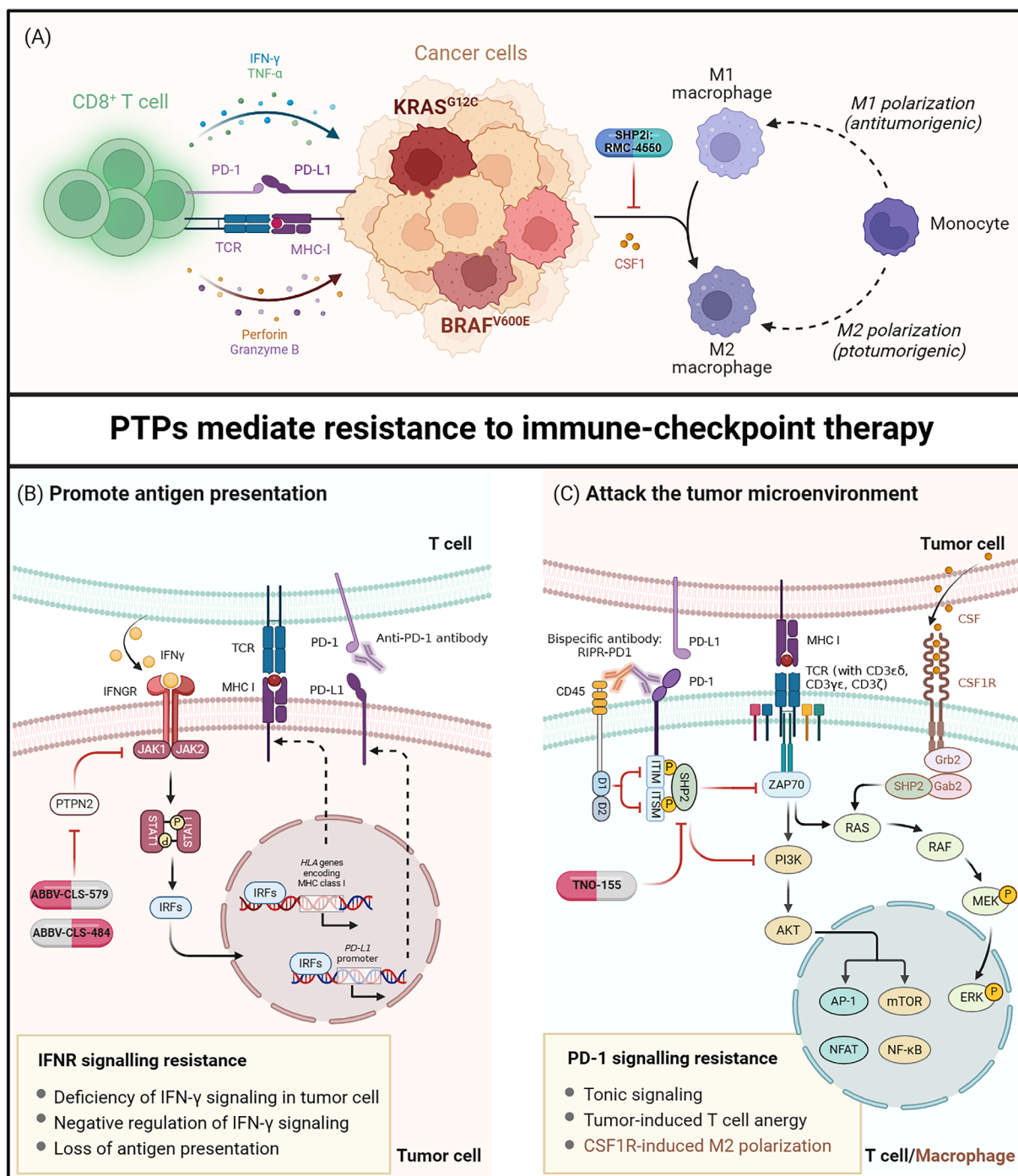
### 3 | PTPs MEDIATE RESISTANCE TO IMMUNE-CHECKPOINT THERAPY

#### 3.1 | SHP2 inhibition in alleviation of colony-stimulating factor-1 (CSF1)-induced resistance to immune-checkpoint blockade

CSF1 is a key regulator to remodel the tumor microenvironment toward immunosuppression by promoting the differentiation of myeloid cells into M2-like tumor-associated macrophages (TAMs) [34]. Programmed death-ligand 1 (PD-L1) expression by TAMs triggered the activation of immune-checkpoint pathways to suppress the cytotoxicity of tumor-specific T cells [35] (Figure 2A). Humanized monoclonal antibodies directed against immune checkpoints were among the most effective cancer therapy in clinic [36, 37]. However, approximately 80% of patients failed to benefit from immunotherapy due to inadequate response or adaptive resistance [38, 39]. Neubert *et al.* [40] examined the gene expression in tumor biopsies from metastatic melanoma patients stratified into responders and non-responders following anti-PD-1 therapy. The non-responders exhibited a positive correlation in gene expression profiles between *CD8A* and *CSF1*, *CSF1* receptor (*CSF1R*), *CD163*, indicating the co-enrichment of CD8<sup>+</sup> T cells with TAMs. This study showed that two major cytokines secreted by activated CD8<sup>+</sup> T cells, IFN- $\gamma$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), were well-known drivers to induce *CSF1* expression in the tumor microenvironment. The *CSF1/CSF1R* signaling in turn drove the recruitment of pro-tumorigenic, M2-like TAMs to human melanoma, thereby contributing to an immunosuppressive microenvironment and limited response to immune-checkpoint therapy (Figure 2A). These findings suggested that T cell-induced *CSF1* expression promoted tumor adaptive resistance to immune-checkpoint therapy [40].

A previous research suggested that SHP2 functioned in a positive manner downstream of *CSF1/CSF1R* signaling to regulate polarization of TAMs toward an immunosuppressive M2 phenotype [41]. It was likely that SHP2 inhibition

**FIGURE 1** PTP inhibition-based combination strategy in combat with drug resistance in targeted therapy. (A) The evolution of drug resistance during the treatment of cancer, including the pre-existing innate resistance and drug-induced acquired resistance. (B) In MAPK pathway driven cancer, feedback activation of SHP2 downstream of EGFR accounted for the molecular mechanism of resistance to targeted therapy. Targeting SHP2 inhibition (TNO-155 or RMC-4630) in combination with MAPK pathway therapeutics (MRTX849, Dabrafenib, etc.) was a potential strategy to overcome clinical resistance in cancer therapy. (C) *DUSP4* and *DUSP6* were functionally redundant genes to regulate downstream ERK phosphorylation. Dual knockout of *DUSP4* and *DUSP6* triggered synthetic lethality in *NRAS* mutant melanoma cells, instead of normal cells or single knockout of *DUSP4/6*. Abbreviations: AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular regulated protein kinase; GDP, Guanosine-5'-diphosphate; GTP, guanosine triphosphate; PDGFR, platelet-derived growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RasGAP, RAS GTPase-activating protein; SHP2, src homology-2 domain-containing phosphatase 2.



**FIGURE 2** The landscape of PTP-mediated pathways in resistance to immune-checkpoint blockade during cancer therapy. (A) Coevolution of cancer progression and anticancer immunity. Cancer cells bearing *KRAS*/*BRAF* mutations were generally immunogenic to activate T cells for immune attack, which was mediated by cell-killing cytokines including IFN-γ, TNF-α, perforin and granzyme B. While cancer cells would express immunosuppressive factors, including PD-L1 and CSF1, to establish immune tolerance through initiation of immune-checkpoint pathways and differentiation of M2-like macrophages. (B) PTPN2 played a negative role in upstream IFN-γ sensing through dephosphorylation of JAKs, leading to loss of antigen presentation in tumor cells. In cancer treatment, targeting PTPN2 inhibition in combination with immune therapy was potential to reverse drug resistance induced by deficiency of IFN-γ sensing. (C) In T cells, SHP2 was downstream of PD-1 to transduce immunosuppressive signal through negative regulation of PI3K-AKT pathway, leading to promotion of T cell anergy. While in macrophages, SHP2 was downstream of CSF1R to promote MAPK pathway driven differentiation of pro-tumorigenic, M2-like macrophage from monocyte. Multiple roles of SHP2 in innate and adaptive immunity eventually evolved into drug resistance mechanism in cancer cell, indicating the potential of targeting SHP2 inhibition in anticancer immune therapy. Besides, bispecific antibody of RIPR-PD-1 was an alternative strategy to recruit CD45 for blockade of tonic signaling mediated drug resistance in immune-checkpoint therapy. Abbreviations: AKT, protein kinase B; AP-1, activator protein-1; CSF-1, colony-stimulating factor-1; CSF1R, colony-stimulating

represented an alternative strategy to abrogate CSF1-mediated resistance to antitumor immunity. Another study found that pharmacologic inhibition of SHP2 with an allosteric inhibitor, RMC-4550, led to significant depletion of CSF1-differentiated bone marrow-derived macrophages [17]. It was attributed that SHP2 inhibition selectively induced caspase-3/7 activation in M2 macrophages, contributing to a profound shift in polarized macrophage populations toward immune susceptibility. Besides, the tumor xenograft model suggested that RMC-4550 induced significant tumor growth delay in CT26 colon carcinoma, whereas anti-CSF1R treatment had minimal effect. These differences in antitumor immunity resulted from that, in addition to CSF1R signaling, SHP2 was also a downstream molecule of PD-1 signaling to restrain T cell immunity [42]. Thus, SHP2 inhibition harbored the potential to induce CD8<sup>+</sup> T cell infiltration and simultaneously impede the resistance dynamics by suppressing CSF1R signaling. Targeting SHP2 inhibition in cancer cells benefited to creating a less immunosuppressive tumor microenvironment susceptible to immunotherapy [43] (Figure 2B). Combination therapy of RMC-4550 and anti-PD-1 antibody resulted in tumor regression in 20% of mice bearing experimental mammary tumour-6 (EMT6) breast carcinoma, and those mice were resistant to subsequent tumor reimplantation, implying long-lasting antitumor immunity [44].

Taken together, the multiple regulatory roles of SHP2 downstream of both CSF1R and PD-1 signaling provided an enormous therapeutic advantage for patients suffering inadequate response or resistance to immune therapy. Clinical trial has initiated the combination regimen of SHP2 inhibitors (TNO-155) and anti-PD-1 antibody (spartalizumab) to evaluate the safety and efficacy in selected malignancies [45]. Meanwhile, rapid development of SHP2 allosteric inhibitors would dramatically accelerate the progression of combination therapy into clinical treatment [46].

### 3.2 | Enforced recruitment of CD45 to block tonic signaling induced immune resistance

Tonic signaling referred to a non-coordinated and sustained activation signaling that accounted for T cell

exhaustion in chimeric antigen receptor T-cell (CAR-T) immunotherapy [47, 48]. Likewise, recent study identified some tonically activated signaling in immune-checkpoint therapy. In Jurkat T cells, application of nivolumab (anti-PD-1 antibody) was efficient to block extracellular ligand-activated signaling, yet it failed to inhibit sustained intracellular downstream signaling, leading to persistent inhibition of T cell function [49]. Furthermore, deletion of the extracellular domain of PD-1 was unable to recapitulate the effect of PD-1 knockout on T cell activation [49]. These results reflected the existence of a ligand-independent mechanism of immune suppression, as evidenced by the phosphorylation of PD-1 in resting T cells [49]. These findings were consistent with previous observations of constitutive phosphorylation of PD-1 immune receptor tyrosine-based switch motif in non-stimulated peripheral blood T cells [50]. Thus, the ligand-independent activation of PD-1 signaling, defined as tonic signaling, accounted for tumor intrinsic resistance to immunotherapy.

CD45 was a receptor-like PTP bearing abundant distribution on the cell surface, resembling the subcellular distribution of immune-checkpoint receptors [51]. To remove tonic signaling-induced intracellular PD-1 phosphorylation, Fernandes *et al.* [49] utilized their overlapped cell distribution to develop a receptor dephosphorylation strategy through enforced recruitment of CD45 to the proximity of PD-1. This approach was termed as receptor inhibition by phosphatase recruitment (RIPR), which referred to a hetero-bispecific antibody RIPR-PD-1 exhibiting binding affinity toward both CD45 and PD-1. RIPR-PD-1 prompted *cis*-ligation between the intracellular phosphatase domain of CD45 and the phosphorylated motifs of PD-1, thus inhibiting both tonic and ligand-activated signaling (Figure 2B). This approach potentiated T cell activation with enhanced expression of CD69 and CD25, as well as the secretion of cytokine IL-12 in T cells. In addition, Fernandes *et al.* [49] also engineered a mouse version of RIPR-PD-1 to substantiate that it was more efficient to reduce tumor volume by approximately 45% than anti-PD-1 antibody in MC38 carcinoma. Therefore, the development of RIPR-PD-1 represented a promising strategy to achieve dual blockade of tonic and ligand-induced signaling in T cells, thereby reversing drug resistance arising from inadequate response to immune-checkpoint therapy.

factor-1 receptor; ERK, extracellular regulated protein kinase; Gab2, Grb2-associated-binding protein 2; Grb2, growth factor receptor-bound protein 2; IFN- $\gamma$ , interferon  $\gamma$ ; IFNGR, interferon- $\gamma$  receptor; IRFs, interferon regulatory factors; ITIM, immune receptor tyrosine-based inhibitory motif; ITSM, immune receptor tyrosine-based switch motif; JAK1/2, Janus kinase 1/2; MEK, mitogen-activated extracellular signal-regulated kinase; MHC-I, major histocompatibility complex class I; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-cells; NF- $\kappa$ B, nuclear factor kappa-B; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; SHP2, src homology-2 domain-containing phosphatase 2; STAT1, signal transducer and activator of transcription 1; TCR, T cell receptor; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; ZAP70, zeta chain of T cell receptor associated protein kinase 70.



### 3.3 | PTPN2 mediate the IFN- $\gamma$ pathway in resistance to immune-checkpoint blockade

Defective mismatch repair-induced genetic lesions have been considered as a central contributor to the development of cancer [52, 53]. High mutational burdens in cancer translated into potential neo-antigens to activate cytotoxic T lymphocytes (CTLs) for the immune attack [54], of which IFN- $\gamma$  played an integral role in antigen presentation [55, 56]. Current clinical trials have substantiated the positive correlation between IFN- $\gamma$  signaling and immune-checkpoint therapy [57–59]. Transcriptome analysis of 101 tumor biopsies from patients with advanced melanoma, being treated with monotherapy of nivolumab (anti-PD-1) or combined with ipilimumab (anti-cytotoxic T lymphocyte associate protein-4, anti-CTLA-4), identified that the expression of IFN- $\gamma$  response genes in tumor-infiltrating T cells were the main drivers of clinical response to immune-checkpoint therapy [57]. The JAK-STAT signaling axis was downstream of interferon- $\gamma$  receptor (IFNGR) to direct the transcriptional activation of IFN- $\gamma$  response genes [60]. Thus, deficiency of the IFN- $\gamma$  pathway resulting from loss-of-function mutations in *JAK1/2* conferred tumor innate resistance to immune-checkpoint therapy [61].

*PTPN2*, encoding T cell-PTP (TC-PTP), was identified as a cancer immunotherapy target due to the antagonistic effect on IFN- $\gamma$  sensing [2]. Manguso *et al.* [2] conducted a pooled loss-of-function genetic screening in melanoma mice treated with anti-PD-1 antibody, and identified that deletion of *PTPN2* rendered susceptibility to immune-checkpoint therapy. Transcriptional analysis of *PTPN2*-null B16 cells revealed a substantial increase in the expression of IFN- $\gamma$  response genes following IFN- $\gamma$  exposure, which increased the level of antigen-loaded major histocompatibility complex class I (MHC-I) on the surface of tumor cells. Then it attracted accumulation of cytotoxic CD8<sup>+</sup> T cells into the tumor microenvironment, leading to significant growth inhibition in melanoma. Knockout *Jak1* or *Stat1* in *PTPN2*-null cells demonstrated a significant growth advantage following anti-PD-1 immunotherapy, indicating that *PTPN2* was upstream of the JAK-STAT axis to modulate IFN- $\gamma$  sensing by tumor cells [2] (Figure 2C). LaFleur *et al.* [62] further dissected that an increase in the number of CTLs could be attributed to the regulation of T cell subpopulation. This study suggested that *PTPN2* deletion promoted differentiation of signaling lymphocytic activation molecule family member 6-positive (Slamf6<sup>+</sup>) progenitor exhausted cells into T cell immunoglobulin domain and mucin domain-3-positive (Tim-3<sup>+</sup>) terminally exhausted cells that were cytotoxic [62]. To evaluate the impact of *PTPN2* on immune-checkpoint therapy, researchers injected MC38 tumor cells into WT or *PTPN2*-

null mice following anti-PD-1 therapy and found that deletion of *PTPN2* resulted in complete tumor clearance, in contrast to the progressive tumor growth observed in WT mice [63]. It reiterated that loss of *PTPN2* rendered tumors more vulnerable to immune-checkpoint therapy.

In conclusion, deficiency in the IFN- $\gamma$  pathway accounted for an integral resistance mechanism to immune therapy [57]. Loss of *PTPN2* abrogated the negative effect of JAK/STAT1 on the expression of IFN- $\gamma$  response genes, increasing IFN- $\gamma$  sensing by tumor cells [2]. Indeed, RNA-sequencing (RNA-seq) analysis of 996 patients with glioma identified that transcriptional level of *PTPN2* was increased in advanced glioma and associated with poor immune response in patients [7]. These findings supported *PTPN2* inhibition as a therapeutic strategy to mitigate resistance to immune therapy. Combination therapy of *PTPN2* inhibitors (ABBV-CLS-484/579) and anti-PD-1 antibodies have progressed into clinical trials to evaluate the safety and efficacy in advanced or metastatic tumors [64].

## 4 | TARGETING PTP INHIBITION TO OVERCOME CANCER THERAPY RESISTANCE

### 4.1 | Targeting PTP inhibition in targeted therapy

Preclinical evidences have substantiated the therapeutic potential of targeting PTP inhibition to combat the emergence of drug resistance in targeted therapy. In clinical trials, it was best characterized by the combination of SHP2 inhibitors in MAPK pathway therapeutics (Table 1). Of note, recruitment of SHP2 was the priority to promote transition of inactive RAS-GDP into active RAS-GTP [12], which made it a crucial convergent node to block abnormal activation of the MAPK pathway, ranging from upstream receptor tyrosine kinases to downstream cascade signaling effectors. Mutations in the *EGFR* gene were the most common feature in patients suffering from relapsed NSCLC [65]. Genetic screening of clinical samples revealed that SHP2 was downstream of EGFR to provide parallel survival input signaling to promote resistance to the third-generation EGFR inhibitors. Preclinical evidences supported the notion that allosteric inhibition of SHP2 could restore sensitivity to EGFR inhibitors in cancers driven by EGFR mutation [43]. A phase I clinical trial of TNO155 in combination with a third-generation EGFR inhibitor, nazartinib, was the first-in-human trial to characterize the safety and tolerability of the combined treatment in EGFR<sup>L858R/T790M</sup> mutant NSCLC (NCT03114319) [66]. The same medication therapy was



TABLE 1 Currently undergoing clinical trials targeting PTPs.

Intervention	NCT	Phase	Treatment protocol	Indication	Status
SHP2 (encoded by <i>PTPN11</i> )					
TNO155	NCT05541159	Phase I (pharmacokinetics study)	TNO155	Renal impairment	Not yet recruiting
	NCT03114319	Phase I	TNO155 plus nazartinib (EGFR inhibitor)	Advanced EGFR mutant NSCLC, KRAS <sup>G12</sup> -mutant NSCLC, esophageal squamous cell carcinoma, head and neck squamous cell carcinoma, melanoma	Recruiting
	NCT04000529	Phase I	TNO155 plus spartalizumab (anti-PD-1 antibody)	NSCLC, esophageal squamous cell carcinoma, head and neck squamous cell carcinoma, gastrointestinal cancer	Recruiting
	NCT04330664	Phase I/II	TNO155 plus MRTX849 (KRAS <sup>G12C</sup> inhibitor)	Advanced or metastatic solid tumor	Recruiting
	NCT04699188	Phase I/II	TNO155 plus JQ443 (KRAS <sup>G12C</sup> inhibitor)	KRAS <sup>G12C</sup> mutant solid tumor, NSCLC, colorectal cancer, pulmonary cancer	Recruiting
	NCT04294160	Phase I	TNO155 plus spartalizumab (anti-PD-1 antibody)	BRF <sup>V600E</sup> colorectal cancer	Recruiting
RMC-4630	NCT03634982	Phase I	RMC-4630	Relapsed/refractory solid tumor	Recruiting
	NCT04916236	Phase I	RMC-4630 plus LY3214996 (ERK1/2 inhibitor)	Pancreatic cancer, colorectal cancer, NSCLC, metastatic KRAS mutant tumor	Recruiting
	NCT05054725	Phase II	RMC-4630 plus sotorasib (KRAS <sup>G12C</sup> inhibitor)	NSCLC with KRAS <sup>G12C</sup> mutation	Active, not recruiting
	NCT03989115	Phase I/II	RMC-4630 plus cobimetinib (MEK inhibitor)	Relapsed/refractory solid tumor	Recruiting
JAB-3068	NCT03518554	Phase I	JAB-3068	EGFR positive locally advanced or metastatic NSCLC	Recruiting
	NCT03565003	Phase I/II	JAB-3068	NSCLC, head and neck squamous cell carcinoma, esophageal cancer, other metastatic solid tumors	Recruiting
JAB-3312	NCT04121286 and NCT04045496	Phase I	JAB-3312	NSCLC, colorectal cancer, pancreatic ductal carcinoma, esophageal squamous cell carcinoma, head and neck squamous cell carcinoma, breast cancer	Recruiting
	NCT05288205	Phase I/IIa	JAB-3312 plus glecirasib (KRAS <sup>G12C</sup> inhibitor)	Advanced solid tumor with KRAS <sup>G12C</sup> mutation	Recruiting
ERAS-601	NCT04670679	Phase I	ERAS-601 plus cetuximab (anti-EGFR antibody)	Advanced or metastatic solid tumor	Recruiting
	NCT04866134	Phase Ib/II	ERAS-601 plus ERAS-007 (ERK inhibitor)	Advanced or metastatic solid tumor	Active, not recruiting
RLY-1971	NCT04252339	Phase I	RLY-1971	Advanced or metastatic solid tumor	Recruiting
SH3809	NCT04843033	Phase I	SH3809	Advanced solid tumor	Recruiting

(Continues)

TABLE 1 (Continued)

Intervention	NCT	Phase	Treatment protocol	Indication	Status
BBP-398	NCT04528836	Phase I	BBP-398	Solid tumor	Recruiting
	NCT05621525	Phase I	BBP-398	Advanced solid tumor, Advanced or metastatic NSCLC	Recruiting
HBI-2376	NCT05375084	Phase I	BBP-398 plus nivolumab (anti-PD-1 antibody)	NSCLC, solid tumor	Recruiting
	NCT05480865	Phase I	BBP-398 plus sotorasib (KRAS <sup>G12C</sup> inhibitor)	Solid tumor, metastatic NSCLC	Recruiting
	NCT06032936	Phase I	BBP-398 plus Osimertinib (EGFR inhibitor)	Advanced or metastatic NSCLC with EGFR mutations	Recruiting
	NCT05163028	Phase I	HBI-2376	NSCLC, colorectal cancer, Pancreatic cancer	Recruiting
HS-10381	NCT05378178	Phase I	HS-10381	Advanced solid tumor	Recruiting
ET0038	NCT05354843	Phase I	ET0038	Advanced solid tumor	Recruiting
BPI-442096	NCT05369312	Phase I	BPI-442096	NSCLC, pancreatic cancer, colorectal cancer	Not yet recruiting
PF-07284892	NCT04800822	Phase I	PF-07284892 plus lorlatinib (ALK inhibitor)	Solid tumor	Active, not recruiting
			PF-07284892 plus binimetinib (MEK1/2 inhibitor)		
			PF-07284892 plus encorafenib (BRAF <sup>V600E</sup> inhibitor)		
			PF-07284892 plus cetuximab (anti-EGFR antibody)		
BR790	NCT05715398	Phase I/IIa	BR790 plus anlotinib (RTKs inhibitor)	NSCLC	Not yet recruiting
	NCT05505877	Phase I/IIa	BR790 plus tislelizumab (anti-PD-1 antibody)	Advanced solid tumor	Recruiting
	NCT06032936	Phase I	BR790 plus osimertinib (EGFR <sup>T790M</sup> inhibitor)	NSCLC	Recruiting
TC-PTP (encoded by <i>PTPN2</i> )					
ABBV-CLS-579	NCT04417465	Phase I	ABBV-CLS-579 PD-1 inhibitor	Locally advanced or metastatic tumor	Recruiting
ABBV-CLS-484	NCT04777994	Phase I	ABBV-CLS-484 PD-1 inhibitor	Relapsed or refractory NSCLC, head and neck squamous cell carcinoma, and advanced clear cell renal cell carcinoma	Recruiting
				Gastric or gastroesophageal junction adenocarcinoma	

Abbreviations: ALK, anaplastic lymphoma kinase; CDK4/6, cyclin-dependent kinase 4/6; EGFR, epidermal growth factor receptor; ERK1/2, extracellular regulated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; RTKs, receptor tyrosine kinases; PTP, protein tyrosine phosphatase.

later found in drug combination including RMC-4630 and osimertinib (NCT03989115) [67], ERAS-601 and cetuximab (NCT04670679) [68]. Downstream of receptor tyrosine kinases, hyperactivation of the RAS-RAF-MEK-ERK signaling axis was observed in a high percentage of tumors, most frequently resulting from activating mutation of *KRAS* and *BRAF* genes [69]. *KRAS* mutants depended on SHP2 phosphatase for cancer progression [16], of which *KRAS*<sup>G12C</sup> mutation was most sensitive to SHP2 inhibition compared to *KRAS*<sup>G13D</sup> and *KRAS*<sup>Q61H</sup> [70, 71]. A couple of phase I/II clinical trials of TNO155 in combination with *KRAS*<sup>G12C</sup> inhibitors, MRTX849 (NCT04330664) or JDQ443 (NCT04699188) [72, 73], were successively initiated to evaluate its molecular effects and clinical efficacy toward advanced solid tumors harboring *KRAS*<sup>G12C</sup> mutation, so was it regarding RMC-4630 and AMG-510 (NCT04185883) [74]. The dependence of class 3 *BRAF* mutants on SHP2-mediated upstream signal for tumor growth conferred sensitivity to SHP2 inhibition [17]. Dual inhibition of SHP2 and *BRAF* was approved to put into clinical trial for advanced and metastatic colorectal cancer with *BRAF*<sup>V600E</sup> mutation (NCT04294160). However, long-term treatment also induced chemoresistance of cancer cells against small-molecule inhibitors [75, 76]. Then inhibition of downstream effectors, MEK or ERK, has been proposed as a complementary strategy [77]. Inhibition of SHP2 activity with RMC-4630 possessed therapeutic potential to synergize with MEK (NCT03989115) or ERK inhibitors (NCT04916236) for the treatment of relapsed and refractory solid tumors resistant to *KRAS* or *BRAF* inhibitors (Table 1) [67, 78]. In summary, targeting SHP2 inhibition in MAPK pathway-driven cancers was expected to be less susceptible to drug resistance in clinical therapy.

Up to date, three clinical trials have released their preliminary safety and efficacy profiles in European Society for Medical Oncology Congress 2023 and World Conference on Lung Cancer 2023. A phase I/IIa clinical trial of glecirasib (*KRAS*<sup>G12C</sup> inhibitor) in combination with JAB-3312 (SHP2 inhibitor) enrolled 144 patients with *KRAS*<sup>G12C</sup> mutated solid tumors (NCT05288205) [79]. Those patients were treated with glecirasib (400 mg or 800 mg daily) in combination with varied doses of JAB-3312. Dose escalation study concluded with one dose-limiting toxicity (DLT), grade 3 pneumonitis, with a rate of 39.8% across all dose levels. Preliminary evaluation in 58 *KRAS*<sup>G12C</sup> NSCLC patients exhibited prominent efficacy as evidenced by a disease control rate (DCR) of 100%. Importantly, the objective response rate (ORR) reached 86.7% in patients administrated with 800 mg glecirasib with 2 mg JAB-3312. Compared to the 37.1% ORR in monotherapy of *KRAS*<sup>G12C</sup> inhibition (NCT03600883) [80], such drug combination regimen manifested promising clinical advantage for NSCLC patients. Subsequent clinical trials

would recruit larger patient cohorts to confirm its efficacy [22]. A phase Ib/II clinical trial of JDQ443 (*KRAS*<sup>G12C</sup> inhibitor) plus TNO155 (SHP2 inhibitor) recruited 50 patients with advanced, *KRAS*<sup>G12C</sup>-mutated solid tumors (NCT04699188) [81]. Those patients received a daily dose of 200 mg JDQ443 in combination with varied doses of TNO155. This combination regimen was well tolerated with a 36% rate of grade 3 treatment-related adverse events (TRAEs), including neutropenia, anemia, and increased creatine phosphokinase. Preliminary anti-tumor effect was observed in enrolled patients, especially NSCLC. Among those NSCLC patients previously treated with *KRAS*<sup>G12C</sup> inhibitor ( $n = 12$ ), the ORR and DCR were 33.3% and 66.7%. In other NSCLC patients received *KRAS*<sup>G12C</sup> inhibitor for the first time ( $n = 12$ ), JDQ443 plus TNO155 yielded an ORR of 33.3% and a DCR of 83.3%. Dose-expansion study is enrolling for future safety and efficacy evaluation [23]. In addition, a phase I/Ib study of RMC4630 (SHP2 inhibitor) and LY3214996 (ERK inhibitor) recruited 11 *KRAS*<sup>G12C</sup>-mutated solid tumors (NCT04916236) [82]. Those patients were divided into 2 cohorts. Cohort 1 was treated with 140 mg RMC-4630 and 100 mg LY3214966. Cohort 2 was treated with 100 mg RMC-4630 and 200 mg LY3214966. Preliminary evaluation identified two instances of DLTs in cohort 1, grade 3 thrombocytopenia and renal insufficiency. Those DLTs limited the tolerability of the combination regimen in cohort 1. By contrast, no DLTs were observed in cohort 2. The ORR in both cohorts was 0%. Patients enrollment is still underway for the evaluation of next dose level [82]. Collectively, phase I/II clinical trials have shown clinical benefit of targeting SHP2 inhibition in *KRAS*<sup>G12C</sup>-mutated solid tumors. If such efficacy could be further confirmed in larger patient cohorts, it is anticipated that these combination regimens would develop as the first-line treatment for *KRAS*<sup>G12C</sup> mutant-driven cancers.

## 4.2 | Targeting PTP inhibition in immune-checkpoint therapy

Immune-checkpoint therapy that blocked extracellular ligand-receptor interaction was unable to persistently suppress intracellular events mediated by phosphatase-dependent tonic signaling. It may account for the inadequate efficacy of immune therapy in clinical treatment [49]. Targeting PTP inhibition in immune-checkpoint therapy represents an efficient strategy to unleash the pre-existing antitumor immunity, transforming a cold tumor into an inflamed one to improve therapeutic response [83]. It was best characterized as synchronous inhibition of extracellular PD-1-PD-L1 interaction and intracellular SHP2 dephosphorylation to overcome tumor-intrinsic resistance to immune-checkpoint blockade [84]. A phase

I clinical trial of TNO155 in combination with anti-PD-1 antibody, spartalizumab, was expected to provide clinical benefit to patients with advanced malignancies (NCT04000529) [85]. In addition, deficiency of the IFN- $\gamma$  pathway was an important resistance mechanism of anti-PD-1 immunotherapy [86]. Preclinical research found that cancer cells resistant to PD-1 blockade became cross-sensitive to *PTPN2* depletion through enhanced IFN- $\gamma$  sensing [2]. Inhibition of *PTPN2* with small-molecule inhibitors, ABBV-CLS-579/484, was expected to restore the efficacy of immune-checkpoint therapy. A phase I clinical trial of ABBV-CLS-579 in combination with PD-1 inhibitor, was the first-in-human trial to characterize the safety and tolerability of combined treatment in locally advanced or metastatic tumors (NCT04417465) [87]. The same medication therapy was later found in drug combination including ABBV-CLS-484 and anti-PD-1 antibody for the treatment of relapsed or refractory gastric or gastroesophageal junction adenocarcinoma (NCT04777994) [88] (Table 1). Therefore, the identification of immunosuppressive PTPs as immune biomarker was necessary to distinguish responsive and non-responsive patients, which provided better guidance on design of immune therapy and the prediction of disease prognosis.

#### 4.3 | The necessary cautionary tale

Despite that emerging evidences supported the conclusion that PTP inhibitors benefited to overcoming drug resistance in cancer therapy, a minority of preclinical studies have found that deletion of PTPs in specific cell types could contribute to accelerated tumor progression. For instance, loss of SHP2 in Kupffer cells and hepatocytes generated a tumor-promoting microenvironment [89]. It resulted from that SHP2 deficiency could trigger apoptosis of Kupffer cells, which in turn induced compensatory recruitment of bone marrow-derived monocytes into the liver. Those monocytes further differentiated into non-Kupffer cells with TAM function, leading to immunosuppressive microenvironment prompt for tumor progression [89]. Another study also found that hepatocyte-specific deletion of SHP2 conferred to hepatic inflammation and necrosis, leading to regenerative hyperplasia and development of hepatocellular carcinoma (HCC) in aged mice [90]. Consistently, decreased SHP2 expression was observed in a subfraction of human HCC specimens [90]. These results raised caution on the application of SHP2 inhibitors in liver cancer therapy. In contrast to the pro-tumorigenic role of *PTPN2* in immune inhibition, overexpression of *PTPN2* in murine epidermis acted as a tumor suppressor to attenuate skin tumor formation [91]. Likewise, examination of human squamous cell carcinoma (SCC) unveiled that

*PTPN2* expression was significantly decreased in advanced stage of SCC [91]. Thus, multiple PTPs harbored double-edged role in regulating carcinogenesis. The design of PTP inhibition-based combination regimens should put cancer type in the first place. In addition, preliminary clinical trials of PTP inhibition-based combination therapy have revealed several grade 3 TRAEs, including pneumonitis, neutropenia, anemia, and increased creatine phosphokinase [22, 23]. Patients with certain underlying diseases who barely tolerate such adverse effects cannot receive those drug combination therapy. As yet, there are none reports indicating that PTP inhibition-based combination regimens are toxic in clinical therapy.

#### 5 | CONCLUSIONS

As a key regulator in tyrosine dephosphorylation of signal transduction proteins, PTP-mediated pathways represent an attractive mechanism for supporting the development of drug resistance. That is, the perturbation of PTPs evolved as an adaptive mechanism of cancer cells to offset stress following anticancer therapy, leading to compromised efficacy of targeted therapy and immune-checkpoint therapy [2, 11]. Preclinical evidences have substantiated that deletion or inhibition of PTPs was sufficient to block sustained activation of growth-stimulatory signaling or create a less immune-suppressive microenvironment [2, 92]. Thus, targeting PTP inhibition in anti-cancer combination therapies seemed to be a potential strategy to overcome clinical resistance.

In clinical settings, there are 3 major challenges in developing PTP inhibition-based combination therapy for the treatment of cancer. The first challenge was the lack of highly potent and specific PTP inhibitors. In concern of the highly conserved and electropositive catalytic pocket in the PTP family, the development of orthosteric inhibitors encountered obstacles in optimizing the bioavailability and selectivity [93]. Alternatively, allosteric inhibitors emerged as a novel strategy to induce or stabilize a catalytically incompetent conformation of PTPs. It was best characterized by the development of highly potent and selective inhibitors of SHP2, such as TNO-155, RMC-4630, and JAB-3312 [94]. Furthermore, blockade of protein-protein interaction between PTPs and upstream molecules was a prominent drug design strategy to circumvent the inherent disadvantage of PTP catalytic pocket. This approach was competent to attenuate the recruitment and activation of PTPs, harboring excellent efficacy similar to that of multidrug combinations. A preclinical research has repurposed the methylene blue, a U.S. Food and Drug Administration-approved chemical for treating methemoglobinemia, as a protein-protein interaction



inhibitor to block the interaction between PD-1 and SHP2 [95]. Followed by development of potent PTP inhibitors, subsequent challenge was how to discover the best drug combinations. In addition to traditional unbiased chemical screens, genome-wide small interfering RNA and CRISPR-Cas9-mediated synthetic lethal drug-sensitization screens benefited to uncovering novel therapeutic combinations targeting PTP inhibition under particular genetic events [96–98]. Nevertheless, genetic screening was incompetent to guide combination therapies targeted at epigenetic alterations of PTPs that rewired signal transduction as a mechanism of resistance. System biology appeared to be an alternative approach to make up for those disadvantages. It was a systemic and network-based biology method integrating multi-omics data including genetic, transcriptomic, and proteomic information into mathematical modeling for predicting the efficacy of potential drug combinations [99, 100]. Once a rationally designed combination was selected, the next challenge was how to implement a drug combination in clinical trials. Thereinto, dose-finding study was a necessary step in the early phase of the clinical setting. It required multiple dose de-escalation cycles to optimize the toxicity-efficacy balance of drug combinations. In cases of narrow therapeutic index of each drug, phase I stage often initiated with dose-finding study to achieve maximal therapeutic effect of combination therapy in clinical trials, while sparing less toxicity [101]. In other cases that full doses of anticancer drugs caused tolerable adverse events, multiple cycles of dose escalation or de-escalation studies were required to find the best stoichiometry ratio between PTP inhibitors and anticancer drugs [3]. Likewise, gleecirasib was identified as a highly selective covalent inhibitor of *KRAS*<sup>G12C</sup>. As reported in the 2022 American Society of Clinical Oncology meeting, gleecirasib exhibited a well-tolerated safety profile with the recommended phase II dose as 800 mg quaque die (QD) (NCT05009329) [102]. Then, phase I/II clinical trial of gleecirasib in combination with JAB-3312 (SHP2 inhibitor) adopted the dose-escalation study to identify the optimal combination dosages (NCT05288205) [22]. Afterward, upon recruiting patients in later clinical trial, defining the disease setting was critical to evaluate the efficacy of PTP inhibition-based drug combination on clinical resistance. In the case that innate resistance to cobimetinib (MEK inhibitor) might be reversed by combination with RMC-4630 (SHP2 inhibitor), the efficacy of combination therapy was best conducted when MEK inhibitor was firstly administrated, instead of in a setting when resistance has already occurred (NCT03989115) [18]. In another case which adaptive resistance to dabrafenib (*BRAF*<sup>V600E</sup> inhibitor) might be overcome by deletion of *DUSP4* and *DUSP6*, intermittent cyclical drug treatment was performed when a part of tumor tissue remained sensitive to dabrafenib, and *DUSP4/6* inhi-

bition was used to target the residual resistant tissue [31]. These cautions highlighted the importance of identifying biomarkers to monitor the clinical process to initiate a combination before the resistance occurred. In-depth research dedicated to overcoming these challenges would accelerate the application of PTP inhibition in combating drug resistance, leading to long-term remission in cancer therapy.

In conclusion, the identification of PTP-mediated pathways in resistance to cancer therapy indicated the future trends of PTP inhibition as the frontline adjuvant therapy. Targeting PTP inhibition in anticancer combination regimens to circumvent drug resistance has achieved certain success in preclinical studies [44, 71]. Currently undergoing clinical trials would further substantiate the efficacy of PTP inhibition-based combination therapies, providing a prominent strategy in our arsenal against drug resistance.

## DECLARATIONS

### AUTHOR CONTRIBUTIONS

Min Zhao, Wen Shuai, and Zehao Su drafted the manuscript under the guidance of Qiu Sun and Guan Wang. Ping Xu and Aoxue Wang revised this manuscript. All authors approved the final version for submission.

### ACKNOWLEDGEMENTS

This manuscript acknowledges financial support from the National Natural Science Foundation of China (82273770 and 22177083), Natural Science Foundation of Sichuan Province (2022NSFSC1290), 135 Project for Disciplines of Excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University (ZYJC21016), and West China Nursing Discipline Development Special Fund Project, Sichuan University (Grant HXHL21011).

### CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

Not applicable.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

### ORCID

Guan Wang  <https://orcid.org/0000-0002-1939-2863>

### REFERENCES

1. Tonks NK. Protein tyrosine phosphatases: from genes, to function, to disease. *Nat Rev Mol Cell Biol.* 2006;7(11):833–846.

2. Manguso RT, Pope HW, Zimmer MD, Brown FD, Yates KB, Miller BC, et al. In vivo CRISPR screening identifies Ptpn2 as a cancer immunotherapy target. *Nature*. 2017;547(7664):413-418.
3. Lopez JS, Banerji U. Combine and conquer: challenges for targeted therapy combinations in early phase trials. *Nat Rev Clin Oncol*. 2017;14(1):57-66.
4. Mustelin T, Vang T, Bottini N. Protein tyrosine phosphatases and the immune response. *Nat Rev Immunol*. 2005;5(1):43-57.
5. Vainonen JP, Momeny M, Westermarck J. Druggable cancer phosphatases. *Sci Transl Med*. 2021;13(588):eabe2967.
6. Ostman A, Hellberg C, Bohmer FD. Protein-tyrosine phosphatases and cancer. *Nat Rev Cancer*. 2006;6(4):307-320.
7. Wang PF, Cai HQ, Zhang CB, Li YM, Liu X, Wan JH, et al. Molecular and clinical characterization of PTPN2 expression from RNA-seq data of 996 brain gliomas. *J Neuroinflammation*. 2018;15(1):145.
8. Dong L, Han D, Meng X, Xu M, Zheng C, Xia Q. Activating mutation of SHP2 establishes a tumorigenic phenotype through cell-autonomous and non-cell-autonomous mechanisms. *Front Cell Dev Biol*. 2021;9:630712.
9. Bollu LR, Mazumdar A, Savage MI, Brown PH. Molecular Pathways: Targeting protein tyrosine phosphatases in cancer. *Clin Cancer Res*. 2017;23(9):2136-2142.
10. Zhang J, Zhang F, Niu R. Functions of Shp2 in cancer. *J Cell Mol Med*. 2015;19(9):2075-2083.
11. Xue JY, Zhao Y, Aronowitz J, Mai TT, Vides A, Qeriqi B, et al. Rapid non-uniform adaptation to conformation-specific KRAS(G12C) inhibition. *Nature*. 2020;577(7790):421-425.
12. Dance M, Montagner A, Salles JP, Yart A, Raynal P. The molecular functions of Shp2 in the Ras/Mitogen-activated protein kinase (ERK1/2) pathway. *Cell Signal*. 2008;20(3):453-459.
13. Easton JB, Royer AR, Middlemas DS. The protein tyrosine phosphatase, Shp2, is required for the complete activation of the RAS/MAPK pathway by brain-derived neurotrophic factor. *J Neurochem*. 2006;97(3):834-845.
14. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: is the undruggable drugged? *Nat Rev Drug Discov*. 2020;19(8):533-552.
15. Bologna-Molina R, Ogawa I, Mosqueda-Taylor A, Takata T, Sánchez-Romero C, Villarroel-Dorrego M, et al. Detection of MAPK/ERK pathway proteins and KRAS mutations in adenomatoid odontogenic tumors. *Oral Dis*. 2019;25(2):481-487.
16. Ruess DA, Heynen GJ, Ciecieski KJ, Ai J, Berninger A, Kabacaoglu D, et al. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. *Nat Med*. 2018;24(7):954-960.
17. Nichols RJ, Haderk F, Stahlhut C, Schulze CJ, Hemmati G, Wildes D, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. *Nat Cell Biol*. 2018;20(9):1064-1073.
18. Fedele C, Ran H, Diskin B, Wei W, Jen J, Geer MJ, et al. SHP2 inhibition prevents adaptive resistance to MEK inhibitors in multiple cancer models. *Cancer Discov*. 2018;8(10):1237-1249.
19. Yang H, Zhou X, Fu D, Le C, Wang J, Zhou Q, et al. Targeting RAS mutants in malignancies: successes, failures, and reasons for hope. *Cancer Commun (Lond)*. 2023;43(1):42-74.
20. Zhao Y, Murciano-Goroff YR, Xue JY, Ang A, Lucas J, Mai TT, et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. *Nature*. 2021;599(7886):679-683.
21. Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, et al. KRAS(G12C) Inhibition with Sotorasib in Advanced Solid Tumors. *N Engl J Med*. 2020;383(13):1207-1217.
22. Wang J, Zhao J, Zhong J, Li X, Fang J, Yu Y, et al. 6530 Glecirasib (KRAS G12C inhibitor) in combination with JAB-3312 (SHP2 inhibitor) in patients with KRAS p.G12C mutated solid tumors. *Ann Oncol*. 2023;34:S459.
23. Negrao MV, Cassier PA, Solomon B, Schuler M, Rohrberg K, Cresta S, et al. MA06.03 KontRASt-01: Preliminary safety and efficacy of JDQ443 + TNO155 in patients with advanced, KRAS G12C-mutated solid tumors. *J Thorac Oncol*. 2023;18(11, Supplement):S117-S118.
24. Setton J, Zinda M, Riaz N, Durocher D, Zimmermann M, Koehler M, et al. Synthetic lethality in cancer therapeutics: the next generation. *Cancer Discov*. 2021;11(7):1626-1635.
25. Wright S, Dobzhansky T. Genetics of natural populations; experimental reproduction of some of the changes caused by natural selection in certain populations of *Drosophila pseudoobscura*. *Genetics*. 1946;31(2):125-156.
26. Mateo J, Porta N, Bianchini D, McGovern U, Elliott T, Jones R, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(1):162-174.
27. Huang A, Garraway LA, Ashworth A, Weber B. Synthetic lethality as an engine for cancer drug target discovery. *Nat Rev Drug Discov*. 2020;19(1):23-38.
28. Yar MS, Haider K, Gohel V, Siddiqui NA, Kamal A. Synthetic lethality on drug discovery: an update on cancer therapy. *Expert Opin Drug Discov*. 2020;15(7):823-832.
29. Yin R, Eger G, Sarri N, Rorsman C, Heldin CH, Lennartsson J. Dual specificity phosphatase (DUSP)-4 is induced by platelet-derived growth factor -BB in an Erk1/2-, STAT3- and p53-dependent manner. *Biochem Biophys Res Commun*. 2019;519(3):469-474.
30. Duan S, Moro L, Qu R, Simoneschi D, Cho H, Jiang S, et al. Loss of FBXO31-mediated degradation of DUSP6 dysregulates ERK and PI3K-AKT signaling and promotes prostate tumorigenesis. *Cell Rep*. 2021;37(3):109870.
31. Ito T, Young MJ, Li R, Jain S, Wernitznig A, Krill-Burger JM, et al. Paralog knockout profiling identifies DUSP4 and DUSP6 as a digenic dependence in MAPK pathway-driven cancers. *Nat Genet*. 2021;53(12):1664-1672.
32. Goetz EM, Ghandi M, Treacy DJ, Wagle N, Garraway LA. ERK mutations confer resistance to mitogen-activated protein kinase pathway inhibitors. *Cancer Res*. 2014;74(23):7079-7089.
33. Leung GP, Feng T, Sigoillot FD, Geyer FC, Shirley MD, Ruddy DA, et al. Hyperactivation of MAPK signaling is deleterious to RAS/RAF-mutant melanoma. *Mol Cancer Res*. 2019;17(1):199-211.
34. Chen YN, LaMarche MJ, Chan HM, Fekkes P, Garcia-Fortanet J, Acker MG, et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. *Nature*. 2016;535(7610):148-152.
35. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat Rev Immunol*. 2019;19(6):369-382.

36. Henriksen A, Dyhl-Polk A, Chen I, Nielsen D. Checkpoint inhibitors in pancreatic cancer. *Cancer Treat Rev*. 2019;78:17-30.
37. Abdou Y, Pandey M, Sarma M, Shah S, Baron J, Ernstoff MS. Mechanism-based treatment of cancer with immune checkpoint inhibitor therapies. *Br J Clin Pharmacol*. 2020;86(9):1690-1702.
38. Shergold AL, Millar R, Nibbs RJB. Understanding and overcoming the resistance of cancer to PD-1/PD-L1 blockade. *Pharmacol Res*. 2019;145:104258.
39. Kalbasi A, Ribas A. Tumour-intrinsic resistance to immune checkpoint blockade. *Nat Rev Immunol*. 2020;20(1):25-39.
40. Neubert NJ, Schmittnaegel M, Bordry N, Nassiri S, Wald N, Martignier C, et al. T cell-induced CSF1 promotes melanoma resistance to PD1 blockade. *Sci Transl Med*. 2018;10(436):eaan3311.
41. Ramesh A, Kumar S, Nandi D, Kulkarni A. CSF1R- and SHP2-inhibitor-loaded nanoparticles enhance cytotoxic activity and phagocytosis in tumor-associated macrophages. *Adv Mater*. 2019;31(51):e1904364.
42. Xu X, Hou B, Fulzele A, Masubuchi T, Zhao Y, Wu Z, et al. PD-1 and BTLA regulate T cell signaling differentially and only partially through SHP1 and SHP2. *J Cell Biol*. 2020;219(6):e201905085.
43. Liu C, Lu H, Wang H, Loo A, Zhang X, Yang G, et al. Combinations with allosteric SHP2 inhibitor TNO155 to block receptor tyrosine kinase signaling. *Clin Cancer Res*. 2021;27(1):342-354.
44. Quintana E, Schulze CJ, Myers DR, Choy TJ, Mordec K, Wildes D, et al. Allosteric inhibition of SHP2 stimulates anti-tumor immunity by transforming the immunosuppressive environment. *Cancer Res*. 2020;80(13):2889-2902.
45. Novartis Pharmaceuticals (Switzerland). (2019, July 30-2024, January 15). Phase Ib study of TNO155 in combination with spartalizumab or ribociclib in selected malignancies. Identifier NCT04000529. <https://clinicaltrials.gov/study/NCT04000529?term=NCT04000529&rank=1>
46. Yuan X, Bu H, Zhou J, Yang CY, Zhang H. Recent advances of SHP2 inhibitors in cancer therapy: current development and clinical application. *J Med Chem*. 2020;63(20):11368-11396.
47. Ajina A, Maher J. Strategies to address chimeric antigen receptor tonic signaling. *Mol Cancer Ther*. 2018;17(9):1795-1815.
48. Chen J, Qiu S, Li W, Wang K, Zhang Y, Yang H, et al. Tuning charge density of chimeric antigen receptor optimizes tonic signaling and CAR-T cell fitness. *Cell Res*. 2023;33(5):341-354.
49. Fernandes RA, Su L, Nishiga Y, Ren J, Bhuiyan AM, Cheng N, et al. Immune receptor inhibition through enforced phosphatase recruitment. *Nature*. 2020;586(7831):779-784.
50. Bardhan K, Aksoylar HI, Le Bourgeois T, Strauss L, Weaver JD, Delcuze B, et al. Phosphorylation of PD-1-Y248 is a marker of PD-1-mediated inhibitory function in human T cells. *Sci Rep*. 2019;9(1):17252.
51. Al Barashdi MA, Ali A, McMullin MF, Mills K. Protein tyrosine phosphatase receptor type C (PTPRC or CD45). *J Clin Pathol*. 2021;74(9):548-552.
52. Li SKH, Martin A. Mismatch repair and colon cancer: mechanisms and therapies explored. *Trends Mol Med*. 2016;22(4):274-289.
53. Shah SN, Hile SE, Eckert KA. Defective mismatch repair, microsatellite mutation bias, and variability in clinical cancer phenotypes. *Cancer Res*. 2010;70(2):431-435.
54. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409-413.
55. Zhou F. Molecular mechanisms of IFN-gamma to up-regulate MHC class I antigen processing and presentation. *Int Rev Immunol*. 2009;28(3-4):239-260.
56. Hoekstra ME, Bornes L, Dijkgraaf FE, Philips D, Pardieck IN, Toebes M, et al. Long-distance modulation of bystander tumor cells by CD8(+) T cell-secreted IFN $\gamma$ . *Nat Cancer*. 2020;1(3):291-301.
57. Grasso CS, Tsoi J, Onyshchenko M, Abril-Rodriguez G, Ross-Macdonald P, Wind-Rotolo M, et al. Conserved interferon- $\gamma$  signaling drives clinical response to immune checkpoint blockade therapy in melanoma. *Cancer Cell*. 2020;38(4):500-515.
58. Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN- $\gamma$ -related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest*. 2017;127(8):2930-2940.
59. Garriss CS, Arlauckas SP, Kohler RH, Trefny MP, Garren S, Piot C, et al. Successful Anti-PD-1 cancer immunotherapy requires T cell-dendritic cell crosstalk involving the cytokines IFN- $\gamma$  and IL-12. *Immunity*. 2018;49(6):1148-1161.
60. Barrat FJ, Crow MK, Ivashkiv LB. Interferon target-gene expression and epigenomic signatures in health and disease. *Nat Immunol*. 2019;20(12):1574-1583.
61. Liu S, Imani S, Deng Y, Pathak JL, Wen Q, Chen Y, et al. Targeting IFN/STAT1 pathway as a promising strategy to overcome radioresistance. *Onco Targets Ther*. 2020;13:6037-6050.
62. LaFleur MW, Nguyen TH, Cox MA, Miller BC, Yates KB, Gillis JE, et al. PTPN2 regulates the generation of exhausted CD8(+) T cell subpopulations and restrains tumor immunity. *Nat Immunol*. 2019;20(10):1335-1347.
63. Katkeviciute E, Hering L, Montalban-Arques A, Busenhardt P, Schwarzfischer M, Manzini R, et al. Protein tyrosine phosphatase nonreceptor type 2 controls colorectal cancer development. *J Clin Invest*. 2021;131(1):e140281.
64. Baumgartner CK, Ebrahimi-Nik H, Iracheta-Vellve A, Hamel KM, Olander KE, Davis TGR, et al. The PTPN2/PTPN1 inhibitor ABBV-CLS-484 unleashes potent anti-tumour immunity. *Nature*. 2023;622(7984):850-862.
65. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121(9):725-737.
66. Novartis Pharmaceuticals (Switzerland). (2017, May 26-2025, May 16). Dose finding study of TNO155 in adult patients with advanced solid tumors. Identifier NCT03114319. <https://clinicaltrials.gov/study/NCT03114319?term=NCT03114319&rank=1>
67. Revolution Medicines, Inc. (U.S.). (2019, July 2-2022, February 8). Dose-esc/exp RMC4630 & Cobi in relapsed/refractory solid tumors & RMC4630 & Osi in EGFR+ locally adv/meta NSCLC. Identifier CT03989115. <https://clinicaltrials.gov/study/NCT03989115?term=NCT03989115&rank=1>
68. Les B. (2020, December 15-2024, May 1). A dose escalation/expansion study of ERAS-601 in patients with advanced or metastatic solid tumors (FLAGSHP-1). Identifier CT04670679. <https://clinicaltrials.gov/study/NCT04670679?term=NCT04670679&rank=1>



69. Samatar AA, Poulikakos PI. Targeting RAS-ERK signalling in cancer: promises and challenges. *Nat Rev Drug Discov.* 2014;13(12):928-942.
70. Gebregiorgis T, Kano Y, St-Germain J, Radulovich N, Udaskin ML, Montes A, et al. The Q61H mutation decouples KRAS from upstream regulation and renders cancer cells resistant to SHP2 inhibitors. *Nat Commun.* 2021;12(1):6274.
71. Lu H, Liu C, Velazquez R, Wang H, Dunkl LM, Kazic-Legoux M, et al. SHP2 inhibition overcomes RTK-mediated pathway reactivation in KRAS-mutant tumors treated with MEK inhibitors. *Mol Cancer Ther.* 2019;18(7):1323-1334.
72. Mirati Therapeutics Inc. (U.S.). (2020, April 22-2024, March 1). Adagrasib in combination with TNO155 in patients with cancer (KRYSTAL 2). Identifier NCT04330664. <https://clinicaltrials.gov/study/NCT04330664?term=NCT04330664&rank=1>
73. Novartis Pharmaceuticals (Switzerland). (2021, February 24-2027, January 8). Study of JDQ443 in patients with advanced solid tumors harboring the KRAS G12C mutation (KontraSt-01). Identifier NCT04699188. <https://clinicaltrials.gov/study/NCT04699188?term=NCT04699188&rank=1>
74. Amgen (U.S.). (2019, December 17-2027, December 31). Sotorasib activity in subjects with advanced solid tumors with KRAS p.G12C mutation (CodeBreak 101). Identifier NCT04185883. <https://clinicaltrials.gov/study/NCT04185883?term=NCT04185883&rank=1>
75. Suzuki S, Yonesaka K, Teramura T, Takehara T, Kato R, Sakai H, et al. KRAS inhibitor resistance in MET-amplified KRAS (G12C) non-small cell lung cancer induced by RAS- and non-RAS-mediated cell signaling mechanisms. *Clin Cancer Res.* 2021;27(20):5697-5707.
76. Wang J, Yao Z, Jonsson P, Allen AN, Qin ACR, Uddin S, et al. A secondary mutation in BRAF confers resistance to RAF inhibition in a BRAF(V600E)-mutant brain tumor. *Cancer Discov.* 2018;8(9):1130-1141.
77. Zhang P, Kawakami H, Liu W, Zeng X, Strebhardt K, Tao K, et al. Targeting CDK1 and MEK/ERK overcomes apoptotic resistance in BRAF-mutant human colorectal cancer. *Mol Cancer Res.* 2018;16(3):378-389.
78. Emile V. (2022, March 31-2024, July 1). Combination therapy of RMC-4630 and LY3214996 in metastatic KRAS mutant cancers (SHERPA). Identifier NCT04916236. <https://clinicaltrials.gov/study/NCT04916236?term=NCT04916236&rank=1>
79. Wang J, Zhao J, Zhong J, Li X, Fang J, Yu Y, et al. 653O Glecirasib (KRAS G12C inhibitor) in combination with JAB-3312 (SHP2 inhibitor) in patients with KRAS p.G12C mutated solid tumors. *Ann Oncol.* 2023;34:S459.
80. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med.* 2021;384(25):2371-2381.
81. Negrao MV, Cassier PA, Solomon B, Schuler M, Rohrberg K, Cresta S, et al. MA06.03 KontraSt-01: Preliminary safety and efficacy of JDQ443 + TNO155 in patients with advanced, KRAS G12C-mutated solid tumors. *J Thorac Oncol.* 2023;18(11, Supplement):S117-S118.
82. Kanhailal AC, Mulero Sanchez A, Knikman JE, Bosma A, Bernards R, Huitema ADR, et al. 1630P Phase I/Ib study of SHP2-ERK inhibition in KRAS<sup>mut</sup> pancreatic cancer (SHERPA trial) and preclinical identification of potential resistance markers. *Annals of Oncology.* 2023;34:S902-S903.
83. Stanford SM, Bottini N. Targeting protein phosphatases in cancer immunotherapy and autoimmune disorders. *Nat Rev Drug Discov.* 2023;22(4):273-294.
84. Liotti F, Kumar N, Prevete N, Marotta M, Sorriento D, Ieranò C, et al. PD-1 blockade delays tumor growth by inhibiting an intrinsic SHP2/Ras/MAPK signalling in thyroid cancer cells. *J Exp Clin Cancer Res.* 2021;40(1):22.
85. Novartis Pharmaceuticals (Switzerland). (2019, July 30-2024, January 15). Phase Ib study of TNO155 in combination with spartalizumab or ribociclib in selected malignancies. Identifier NCT04000529. <https://clinicaltrials.gov/study/NCT04000529?term=NCT04000529&rank=1>
86. Yu M, Peng Z, Qin M, Liu Y, Wang J, Zhang C, et al. Interferon- $\gamma$  induces tumor resistance to anti-PD-1 immunotherapy by promoting YAP phase separation. *Mol Cell.* 2021;81(6):1216-1230.e9.
87. Calico Life Sciences LLC (U.S.). (2020, June 3-2026, April 30). First in human study with ABBV-CLS-579 when given alone and in combination in participants with locally advanced or metastatic tumors. Identifier NCT04417465. <https://clinicaltrials.gov/study/NCT04417465?term=NCT04417465&rank=1>
88. Calico Life Sciences LLC (U.S.). (2021, March 9-2026, October 5). A Phase 1 study with ABBV-CLS-484 in subjects with locally advanced or metastatic tumors. Identifier NCT04777994. <https://clinicaltrials.gov/study/NCT04777994?term=NCT04777994&rank=1>
89. Du L, Ji Y, Xin B, Zhang J, Lu LC, Glass CK, et al. Shp2 deficiency in Kupffer cells and hepatocytes aggravates hepatocarcinogenesis by recruiting non-Kupffer macrophages. *Cell Mol Gastroenterol Hepatol.* 2023;15(6):1351-1369.
90. Bard-Chapeau EA, Li S, Ding J, Zhang SS, Zhu HH, Princen F, et al. Ptpn11/Shp2 acts as a tumor suppressor in hepatocellular carcinogenesis. *Cancer Cell.* 2011;19(5):629-639.
91. Kim M, Morales LD, Lee CJ, Olivarez SA, Kim WJ, Hernandez J, et al. Overexpression of TC-PTP in murine epidermis attenuates skin tumor formation. *Oncogene.* 2020;39(21):4241-4256.
92. Liu M, Gao S, Elhassan RM, Hou X, Fang H. Strategies to overcome drug resistance using SHP2 inhibitors. *Acta Pharm Sin B.* 2021;11(12):3908-3924.
93. Stanford SM, Bottini N. Targeting tyrosine phosphatases: time to end the stigma. *Trends Pharmacol Sci.* 2017;38(6):524-540.
94. Song Z, Wang M, Ge Y, Chen XP, Xu Z, Sun Y, et al. Tyrosine phosphatase SHP2 inhibitors in tumor-targeted therapies. *Acta Pharm Sin B.* 2021;11(1):13-29.
95. Fan Z, Tian Y, Chen Z, Liu L, Zhou Q, He J, et al. Blocking interaction between SHP2 and PD-1 denotes a novel opportunity for developing PD-1 inhibitors. *EMBO Mol Med.* 2020;12(6):e11571.
96. McDonald ER, 3rd, de Weck A, Schlabach MR, Billy E, Mavrikis KJ, Hoffman GR, et al. Project DRIVE: A Compendium of cancer dependencies and synthetic lethal relationships uncovered by large-scale, deep RNAi screening. *Cell.* 2017;170(3):577.
97. Haley B, Roudnicki F. Functional genomics for cancer drug target discovery. *Cancer Cell.* 2020;38(1):31-43.
98. Weber J, Braun CJ, Saur D, Rad R. In vivo functional screening for systems-level integrative cancer genomics. *Nat Rev Cancer.* 2020;20(10):573-593.



99. Cheng F, Kovács IA, Barabási AL. Network-based prediction of drug combinations. *Nat Commun.* 2019;10(1):1197.
100. Ryall KA, Tan AC. Systems biology approaches for advancing the discovery of effective drug combinations. *J Cheminform.* 2015;7:7.
101. Liao JJZ, Zhou F, Zhou H, Petruzzelli L, Hou K, Asatiani E. A hybrid design for dose-finding oncology clinical trials. *Int J Cancer.* 2022;151(9):1602-1610.
102. Li J, Zhao J, Cao B, Fang J, Li X, Wang M, et al. A phase I/II study of first-in-human trial of JAB-21822 (KRAS

G12C inhibitor) in advanced solid tumors. *J Clin Oncol.* 2022;40(16\_suppl):3089.

**How to cite this article:** Zhao M, Shuai W, Su Z, Xu P, Wang A, Sun Q, et al. Protein tyrosine phosphatases: emerging role in cancer therapy resistance. *Cancer Commun.* 2024;44:637–653. <https://doi.org/10.1002/cac2.12548>