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The Efficacy and Safety of *FGFR*-Selective Inhibitors for Cancer Patients

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Abstract

The Fibroblast Growth Factor Receptor (*FGFR*) signaling pathway is closely related to the development of various biological processes. It has been found that dysregulation of *FGFR* signaling leads to cell proliferation, migration, angiogenesis, and immune evasion, all of which contribute to tumor occurrence and development. Tumor precision therapy is targeted treatment based on the driver gene. *FGFR* represents a novel and promising therapeutic target for tumor treatment in precision medicine. *FGFR* aberrations exist in a variety of tumors. By applying Next-Generation Sequencing (NGS), it is now possible to identify patients who are candidates for therapies targeting *FGFR*. Current evidence suggests that *FGFR* Tyrosine Kinase Inhibitors (TKIs) have demonstrated benefits for certain types of cancer patients and are approved by the FDA for the treatment of *FGFR*-dysregulated cancers. Although *FGFR*-TKIs have shown promise, they have encountered several problems, including acquired resistance and side effects. In this article, we will focus on *FGFR*-TKIs and their role in treating cancers with altered *FGFR*s, as well as summarize the challenges and solutions involved in their use.

Keywords: *FGFR*; Signal pathway; Targeted therapy; *FGFR* inhibitors; Acquired resistance

Introduction

Targeted therapy has become a typical representative of the age of tumor precision medicine. Tumor growth and progression are inhibited and blocked by many targeted therapies. There are a number of approaches that target tyrosine kinase receptors. Targeted therapy for Epidermal Growth Factor Receptor (EGFR) in non-small cell lung cancer is a successful example. Targeting the FGF/*FGFR* signaling axis is a promising therapeutic strategy, and many tumor types have been successfully treated with Tyrosine Kinase Inhibitors (TKIs) that block the FGF/*FGFR* signaling axis. A number of biological processes involve the *FGFR* signaling pathway, including embryogenesis, cell differentiation, proliferation, migration, and angiogenesis [1]. *FGFR* aberrations, including gene amplification, mutation, and gene fusion, result in abnormal activation of the *FGFR* signaling pathway, all of which are observed in malignant tumors such as urothelial carcinoma and cholangiocarcinoma and are potential targets for cancer therapeutics [2]. It is likely that abnormally activated *FGFR* signaling leads to tumor cell proliferation, invasion and migration as well as tumor angiogenesis. In addition, the *FGFR* signaling pathway also plays an essential role in escape mechanisms and acquired resistance to anticancer therapies.

With the application of Next-Generation Sequencing (NGS), an increasing number of *FGFR* aberrations have been detected. A growing number of *FGFR* tyrosine kinase inhibitors are under clinical study based on NGS detection results for multiple tumor types. Several clinical studies in different tumors have shown promising results in blocking the *FGFR* signaling pathway with TKIs [3]. Along with the popularity of clinical application, *FGFR* inhibitors also have some disadvantages, such as systemic toxicity and acquired drug resistance, which limit the clinical application of *FGFR* inhibitors. The development and combination of new *FGFR* inhibitors are effective measures to solve systemic toxicity and acquired drug resistance. To assess the therapeutic value of targeting the *FGFR* axis by TKIs in tumors, this review will first discuss the normal structure and function of *FGFR*. Then, we will discuss the recent improvements in selective *FGFR* inhibitors, as well as nonselective *FGFR* inhibitors, and explore the mechanism of drug resistance.

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Structure and function of *FGFR*

By interacting with their receptors, Fibroblast Growth Factors (FGFs) coordinate multiple cellular processes. On the basis of sequence similarity and phylogeny, the FGF/*FGFR* family includes 22 factors that bind to five *FGFR*s in humans [4-6]. A conservation core of 120 amino acids is found in each FGF ligand, ranging from 35% to 50% sequence homology, which can be widely divided into hormonal and canonical isoforms according to its mechanism of action and *FGFR* binding [5,7]. Only the hormonal subtypes can spread into the blood vessels and bind to *FGFR* when klotho proteins are present, thus functioning as appropriate endocrine molecules to affect homeostasis and metabolism in adults [8,9]. The canonical subtypes integrate with *FGFR* by heparin sulfate glycosaminoglycan and act in an autocrine/paracrine manner.

There are five different receptors in the *FGFR* family, *FGFR1*-5, which are encoded by *FGFR1-4* and *FGFR*L1, respectively, and only *FGFR1-4* expresses tyrosine kinases on cell membranes with 56% to 71% homology [6,10,11]. It consists of extracellular immunoglobulin-like domains [1-3], a transmembrane domain, an intracellular tyrosine kinase domain, a carboxyl-terminal region, and an acidic region [12]. By binding the FGF ligand to *FGFR*, *FGFR* dimerization is triggered, which in turn phosphorylates *FGFR* Substrate 2 (FRS2). By activating downstream signaling pathways, including Phosphoinositide-3-Kinase (PI3K) and Mitogen-Activated Protein Kinase (MAPK), FRS2 promotes cell proliferation [13]. As a result of *FGFR* activation, the Phospholipase C gamma (PLC-gamma) and Signal Transducer and Activator of Transcription (STAT) signaling pathways are also triggered (Figure 1) [14]. Different ligands and receptors determine different physiological functions of FGF-*FGFR* pathways. *FGFR1-4* plays a crucial role in embryogenesis, cell cycle regulation, and angiogenesis. Additionally, *FGFR4* is involved in glucose homeostasis, bile acid metabolism, and vitamin D synthesis [15,16].

A malfunctioning *FGFR* signaling system caused by gene amplification, mutations, and gene fusions is likely to promote cell proliferation, migration, and angiogenesis in cancer cells, which are potential targets for anticancer therapies [17]. An analysis of over 4,800 tumor samples revealed that 7.1% of tumors had *FGFR* abnormalities [18]. *FGFR* alterations were most common in urothelial carcinomas (32%), breast cancers (18%), endometrial cancers (13%), and lung squamous cell carcinomas (13%). A majority of *FGFR* alterations were gene amplification (66%), followed by mutation (26%) and rearrangement (8%).

FGFR tyrosine kinase inhibitors (TKIs)

In terms of mechanism, *FGFR* inhibitors are divided into different categories: *FGFR* Tyrosine Kinase Inhibitors (TKIs) that block the intracellular activity of *FGFR* and are small molecule inhibitors, Monoclonal Antibodies (MABs) that target *FGFR*, traps for FGF ligands and Antibody Drug Conjugates (ADCs).

FGFR-TKIs mainly inhibit the intracellular tyrosine kinase domains, while *FGFR* monoclonal antibodies target *FGFR* extracellular domains with better isotype selectivity and are a promising target for development. *FGFR* monoclonal antibodies inhibit *FGFR* and its downstream signaling pathways by interfering with the binding of the ligand FGF to the receptor or blocking *FGFR* dimerization. Currently, a variety of *FGFR* monoclonal antibodies are under clinical studies, such as Bemarituzumab. Because *FGFR* monoclonal antibodies act only on specific *FGFR* subtypes in the extracellular domain, they have higher specificity and no off-target effects, resulting in fewer adverse drug reactions compared to small molecule *FGFR* inhibitors. Unlike small molecule tyrosine kinase inhibitors and monoclonal antibodies that directly act on *FGFR*, the mechanism of the FGF ligand trap is to trap and isolate free FGFS and block it's binding to corresponding receptors, thus achieving the purpose of inhibiting the *FGFR* downstream signaling pathway. At present, a variety of FGF ligand traps are in the clinical research stage, such as FP-1039. Antibody-Drug Conjugates (ADCs) are a class of drugs that conjugate cytotoxic drugs with biological activity to monoclonal Antibodies (mAbs) by chemical bonds. Monoclonal Antibodies (mAbs) act as carriers to transport cytotoxic drugs to target cells. ADCs have the lethal power of cytotoxic drugs and combine the high targeting, stability and favorable pharmacokinetic characteristics of recombinant mAbs.

This paper mainly describes the progress of *FGFR*-TKIs. *FGFR*-TKIs consist of nonselective multitargeted inhibitors that inhibit *FGFR*, VEGF and PDGF as well as other tyrosine kinases in a nonselective manner and selective *FGFR* inhibitors that specifically inhibit *FGFR1-4*.

Nonselective multitargeted inhibitors

Multitargeted kinase *FGFR* inhibitors are first-generation *FGFR* inhibitors that not only bind to *FGFR1-4* in a competitive and reversible manner but also show nonselective inhibitory activity against other tyrosine kinases, such as Vascular Endothelial Cell Growth Factor Receptors (VEGFR), Platelet-Derived Growth Factor Receptors (PDGFR), FMS-Like Tyrosine kinase-3 (FLT-3), Removable Exon Trap (RET), and c-KIT19. Nonselective multitargeted inhibitors targeting the *FGFR* signaling pathway are available, such as dovitinib, nintedanib, ponatinib, regorafenib, pazopanib, and Lenvatinib.

Some multitargeted *FGFR* inhibitors have been approved by the Food and Drug Administration (FDA) for treating cancer. Unresectable advanced renal cancer, liver cancer, and thyroid cancer can be treated with sorafenib, which has been approved by the FDA, whereas sunitinib is indicated for the treatment of gastrointestinal stromal tumors, advanced renal cell carcinoma, and pancreatic neuroendocrine tumors. Furthermore, regorafenib has been approved to treat a number of cancers, including advanced colorectal cancer and gastrointestinal stromal tumors. As a multitargeted TKI, pazopanib inhibits the action of *FGFR*, VEGFR, PDGFR and c-KIT. According to FDA approval, the drug improves Progression-Free Survival (PFS) compared to placebo (4.6 months *vs.* 1.6 months) for the second-line treatment of soft tissue tumors [20,21].

In clinical trials, several multitargeted inhibitors of *FGFR* are being tested. Dovitinib is a nonselective inhibitor of *FGFR*, PDGFR, VEGFR, and c-KIT that has been shown to be effective in phase II/III clinical trials as a second-line treatment in patients refractory to imatinib with a disease control rate of over 50% at 12 weeks [22,23]. A nonselective TKI for *FGFR* is ponatinib, which inhibits *FGFR*, KIT, RET, VEGFR and PDGFR, which inhibits *FGFR* downstream signaling pathways and shows strong activity with a more than 45% disease response rate in advanced cholangiocarcinoma treatment [24]. Similarly, anlotinib targets several members of the tyrosine kinase family, including *FGFR1*, PDGFR, DGFR, and c-KIT, due to a lack of drug selectivity, and is approved as a second-line treatment for advanced non-small cell lung cancer and soft tissue tumors [25].

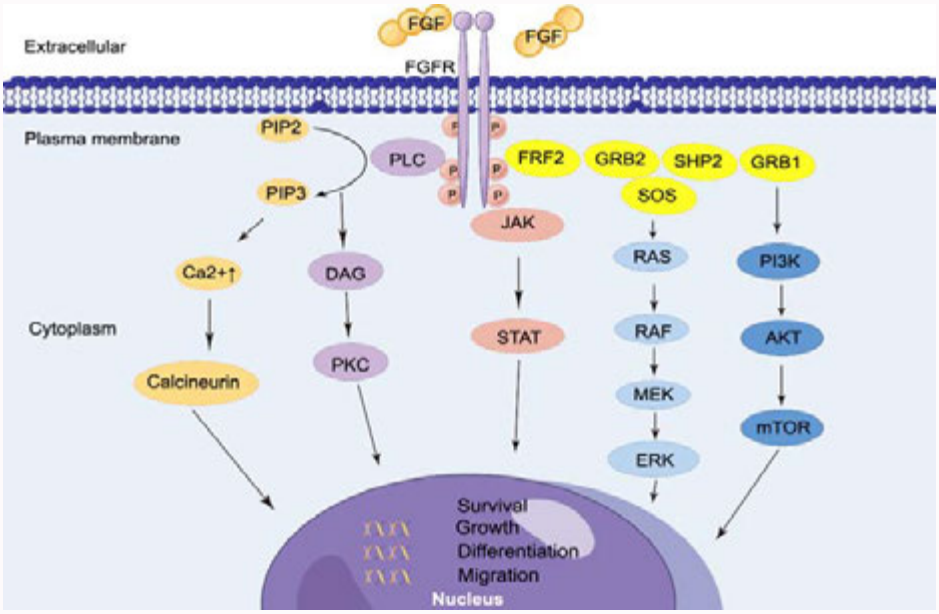

Figure 1: FGF-*FGFR* signaling pathway. The binding of FGFs stimulates *FGFRs* dimerization, resulting in cellular survival, growth, differentiation and migration through Ras-Raf-MAPK, PI3K-AKT, PLCγ and STATs pathways. (See the manuscript for more details) (Created by Figdraw).

The advantage of multitargeted *FGFR* inhibitors is that they have a wide range of targets, which inhibits a variety of cancers with associated targets. However, due to their low selectivity and strong dependence on the inhibition of VEGFR and PDGFR, multitargeted *FGFR* inhibitors show high side effects, including hypertension, fatigue, and gastrointestinal reactions, so the clinical use of multitargeted *FGFR* inhibitors is limited. Therefore, the development of selective inhibitors that target *FGFR* is essential and a hot spot right now.

Selective *FGFR* inhibitors

A number of limitations exist in traditional multitargeted *FGFR* inhibitors, including off-target effects, treatment-related side effects, and acquired resistance. Recently, some types of tumors have been treated with inhibitors that selectively target *FGFR* for antitumor treatment. Based on their spatial configuration and the conformation they engage upon binding to their target kinase, selective *FGFR* inhibitors can be classified into two types: Noncovalent *FGFR* inhibitors and covalent *FGFR* inhibitors. In contrast to noncovalent *FGFR* inhibitors, covalent *FGFR* inhibitors are irreversible. Some selective *FGFR* inhibitors are being tested in clinical trials, as shown in Table 1. First-generation noncovalent selective *FGFR* inhibitors (pan-*FGFR* inhibitors) were Erdafitinib, Infigratinib, Pemigatinib, and Rogaratinib, which inhibited *FGFR1-4*.

Noncovalent *FGFR* inhibitors

Erdafitinib is an ATP-competitive inhibitor that inhibits *FGFR1-4*. Erdafitinib [NCT01703481] was studied in 187 patients, 92 of whom had aberrant *FGFR*, and of these, 19 (21%) showed partial responses. The response rates were 27% and 46%, respectively in cholangiocarcinoma and urothelial cancer patients harboring a mutant or fusion form of *FGFR2*-3 [26]. In a phase II trial [NCT02365597], Erdafitinib was evaluated for its antitumor effect in locally advanced or metastatic urothelial cancer that was resistant to platinum-containing therapies. A total of 99 patients with *FGFR2*/*FGFR*3 alterations had an objective response rate of 40% (CR: 3%, PR: 37%), a median Progression-Free Survival (PFS) of 5.5 months, and a median Overall Survival (OS) of 13.8 months [27]. Hyperphosphatemia is the most common adverse effect. On the basis of the above evidence, Erdafitinib received FDA approval.

The drug pemigatinib inhibits *FGFR1-3* in an ATP-competitive manner and is approved as a second-line treatment for biliary duct cancer. In the phase II study FIGHT-202 [NCT02924376], pemigatinib was investigated in cholangiocarcinoma's that had progressed to standard treatment. An ORR of 35.5% (CR: 2.8%, PR: 32.7%), median Progression-Free Survival (PFS) of 6.9 months, and median Duration of Response (DOR) of 7.5 months were observed in 107 patients harboring fusions and rearrangements of *FGFR2* [28]. The common adverse effects include hyperphosphatemia, stomatitis and arthritis.

The ATP-competitive inhibitor 31 of *FGFR1-3*, Infigratinib, is used for the treatment of cancer. A phase II clinical trial [NCT02150967] enrolled 61 patients harboring *FGFR1-3* mutations after progression on first-line treatment for cholangiocarcinoma [29]. Regarding genetic alterations, *FGFR2* fusion (48/61) and *FGFR2* mutation (8/61) were the most common. The clinical study showed that the ORR of Infigratinib was 14.8%, and the median PFS was 5.8 months. Infigratinib was obtained FDA approval in light of its favorable clinical trial results. The common adverse reactions in the course of treatment are hyperphosphatemia, stomatitis and fatigue. Several clinical studies evaluating the efficacy of Infigratinib in urothelial carcinoma and gastrointestinal stromal tumors are being carried out.

FGFR1-4 is inhibited by rogaratinib through ATP competition. According to a phase I trial [NCT01976741], rogaratinib had an ORR of 22.9% in 51 patients with *FGFR1-3*-overexpressing urothelial carcinoma [30]. It was also found that benefits were observed in head and neck squamous cell carcinomas and non-small cell lung cancers. In the FORT-1 [NCT03410693] phase II/III study, following standard first-line treatment; rogaratinib achieved an ORR of 52.4% in urothelial carcinoma patients with *FGFR3* mutation or fusion [31]. As a first-line treatment for urothelial carcinoma, rogaratinib

Table 1: Selective *FGFR* inhibitors in ongoing clinical trials.

Agent	Targets	Tumors	Phase	Study Identifier
Derazantinib	*FGFR1-4*	Solid Tumor	I/II	NCT01752920
RLY-4008	*FGFR2*	Solid Tumors	I/II	NCT04526106
Erdafitinib	*FGFR1-4*	NSCLC	II	NCT03827850
Debio 1347	*FGFR1-3*	Solid Tumor	II	NCT03834220
3D185	*FGFR1-3*	Solid Tumors	I	NCT04221204
pemigatinib	*FGFR1-3*	Gastric/Colorectal Cancer	II	NCT05202236
SY-4798	*FGFR4*	Solid Tumor	I	NCT05498519
AZD4547	*FGFR1-3*	IDH wild type Gliomas	I/II	NCT02824133
ET0111	*FGFR1-4*	Solid Tumors	I	NCT05522309
Futibatinib	*FGFR1-4*	liver cancer	II	NCT04828486

combined with atezolizumab was evaluated in another clinical trial [NCT03473756] [32]. The ORR was 44% among 31 patients with *FGFR* mRNA overexpression.

Debio-1347, or zoligratinib, is an oral selective ATP-competing inhibitor of *FGFR* 1-3 tyrosine kinase. A Pan tumor phase I study evaluated the efficacy and safety of Debio-1347 in patients with advanced solid tumors fusing *FGFR 1-3* [33]. Of the 5 patients with cholangiocarcinoma enrolled in the trial, 4 carried *FGFR2* fusion. All 4 patients had disease control, 2 had partial response, and 2 had stable disease. The most common adverse events were hyperphosphatemia (76%), diarrhea (41%), nausea (40%), fatigue (38%), and constipation (33%). In addition, the Phase II basket trial FUZE will evaluate the efficacy and safety of Debio-1347 in patients with solid tumors containing *FGFR1-3* gene fusion [NCT03834220].

Other selective noncovalent *FGFR* inhibitors are in clinical trials, such as Ly2874455 and AZD4547. Although selective noncovalent *FGFR* inhibitors showed improved targeting and significantly reduced adverse reactions compared to nonselective *FGFR* inhibitors, the clinical application of selective noncovalent *FGFR* inhibitors is still limited by acquired resistance and adverse effects.

Covalent *FGFR* inhibitors

A number of studies have revealed that mutations at the gatekeeper residue of *FGFR* are the main cause of resistance to selective noncovalent *FGFR* inhibitors in different tumor types [34,35]. The covalent inhibition strategy is an effective way to overcome mutations that act as gatekeepers [36]. Common covalent *FGFR* inhibitors include fisogatinib, futibatinib and roblitinib.

Inhibitors of *FGFR4*, such as fisogatinib, are irreversible covalent compounds. An ORR of 17% was reported in a phase I trial of fisogatinib in patients with hepatocellular carcinoma expressing FGF19 (NCT02508467) [37]. The FDA granted fisogatinib orphan drug status for treating hepatocellular carcinoma based on this evidence [38]. The covalent inhibitor futibatinib inhibits *FGFR1-4* in an irreversible manner.

FGFR2 genetically altered patients with unresectable or advanced hepatocellular carcinoma who had received at least first-line treatment are recruited for FOENIX-CCA2 [NCT02052778]. Patients with *FGFR2* fusions had an ORR of 36.2%, while those with *FGFR2* rearrangements had an ORR of 44.4% [39,40]. For this reason, futibatinib has been approved for the second-line treatment of advanced hepatocellular carcinoma by the FDA. There is a covalent inhibitor of *FGFR4* called roblitinib. The *FGFR4* inhibitor exhibited good efficacy with a Disease Control Rate (DCR) of 61% in hepatocellular carcinoma and other solid tumors that expressed the receptor. The median time to progression is up to 4.1 months [11,41].

Resistance to *FGFR*-TKIs

Despite the demonstrated potential of *FGFR*-TKI targeted therapy, resistance to *FGFR*-TKIs and exploring ways to overcome drug resistance are becoming increasingly important. Several studies have suggested that the mechanism of *FGFR*-TKI resistance in cancer is complex and mainly includes the occurrence of secondary *FGFR* genes and activation of bypass signaling pathways [42,43].

The primary mechanism of resistance to *FGFR*-TKIs in targeted therapy is secondary mutations in the *FGFR* gene, particularly at gatekeeper residues [42]. As part of the ATP binding pocket, the gatekeeper residue in the hinge region participates in regulating TKIs and activating the conformation of kinases [44]. It is critical to develop pan-*FGFR* inhibitors, such as LY2874455, that have binding sites that are not in the hinge region of the receptor, especially where the gatekeeper residues are located. Resistance based on mutation may be overcome by inhibiting mutant *FGFR* gatekeepers [45]. In contrast to gatekeeper mutations, other gene mutations are relatively fewer but still important. As an example, the *FGFR1* N546K mutation promotes ATP binding, resulting in resistance to *FGFR*-TKIs [35]. In the presence of the E565A mutation of *FGFR2*, the PI3K signaling pathway can be activated [46].

As a result of resistance to *FGFR* inhibitors, PI3K-AKT signaling pathway activation and RAS-MAPK signaling pathway activation are also important mechanisms [43]. In *FGFR* inhibitor-resistant cell lines, AKT phosphorylation levels increased significantly, which could be reversed by AKT inhibitors and recovered *FGFR* inhibitor sensitivity [47]. Activated RAS-MAPK signaling pathways that stimulate cancer cell growth and bypass *FGFR* inhibition are also crucial factors in drug resistance [48,49]. Furthermore, *FGFR*-TKI resistance is associated with the activation of membrane receptor tyrosine kinases, including ErbB3, MET, and EGFR [42]. To overcome resistance, it is important to improve the efficiency of kinase inhibitors.

The combination of inhibitors with different signaling pathways is a feasible strategy for blocking alternatively activated signaling [50]. The combination of *FGFR* inhibitors and immune checkpoint inhibitors has been studied in clinical trials for efficacy and safety [51]. Although combination targeted therapy shows some potential, it may cause more adverse drug reactions. Hence, a single compound with a binocular target is a promising development direction [52]. Inhibiting multiple signaling pathways, such as PIK3C3 and *FGFR*, is one of the latest therapeutic approaches, such as MPT0L145 [53].

Conclusion and Perspective

Because the *FGFR* signaling pathway has been implicated in multiple stages of cancer development, *FGFR* is a promising target for cancer treatment. Tumor precision therapy is a targeted treatment based on the driver gene, and targeting the *FGFR* signaling pathway is a typical example due to the detection of *FGFR* targets and the application of selective *FGFR* inhibitors. Currently, multitargeted *FGFR* inhibitors are widely used in tumor-targeted treatment. A number of selective *FGFR* inhibitors have been approved by the FDA, which will stimulate clinical trials of other selective *FGFR* inhibitors.

It is challenging to apply *FGFR* inhibitors in clinical settings due to the emergence of acquired resistance and the absence of

appropriate screening for patients. The *FGFR* signaling pathway should be screened in a variety of tumors, especially those with a high aberration frequency. The application of Next-Generation Sequencing (NGS) has normalized the selection of suitable patients for *FGFR*-targeted therapy. Meanwhile, appropriate biomarkers should be identified by NGS to select the most appropriate *FGFR* inhibitors for optimal efficacy. Identifying the mechanisms of acquired resistance by molecular detection is key to overcoming resistance. For example, for the activation of the bypass signaling pathway, combination treatment is a feasible strategy. In addition, the development of a single compound with a dual target is also a promising direction for better efficacy and fewer side effects.

In conclusion, targeted therapy for *FGFR* is an important link in the field of targeted oncology. Ongoing clinical trials are expected to speed up *FGFR*-TKI approval for all kinds of tumor patients with *FGFR* aberrations.

Author Contributions

Conceptualization: Wei Du. Data curation: Yuxin Xie, Xueming Xia. Project administration: Qiheng Gou. Supervision: Qiheng Gou. Writing-original draft: Xueming Xia. Revision: Qiheng Gou, Wei Du, Xueming Xia. All authors made a significant contribution to the work reported gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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