Focal Adhesion Kinase Inhibitors

Subjects: Pathology

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Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase over-expressed and activated in both adult and pediatric cancers, where it plays important roles in the regulation of pathogenesis and progression of the malignant phenotype. FAK exerts its functions in cancer by two different ways: a kinase activity in the cytoplasm, mainly dependent on the integrin signaling, and a scaffolding activity into the nucleus by networking with different gene expression regulators. For this reason, FAK has to be considered a target with high therapeutic values. Indeed, evidence suggests that FAK targeting could be effective, either alone or in combination, with other already available treatments.

FAK adult cancers pediatric cancers targeted therapy combination therapy PROTACs ATP-competitive inhibitors allosteric inhibitors

1. Introduction

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase with a molecular weight of 125 kDa that contributes to the regulation of different cellular processes, including cell survival, proliferation, apoptosis, adhesion, migration and mechano-transduction (ref. [1] and reviewed in [2]). The FAK gene, also known as protein tyrosine kinase 2 (PTK2), maps onto the human chromosome 8q24.3 region and encodes for the FAK protein that is ubiquitously expressed in different types of cells, with a prevalent localization in the plasma membrane and cytoplasm. FAK was described for the first time in 1992 by Schaller et al. as a central protein associated to the sub-cellular structures named focal adhesions (FAs), which regulate signaling events in response to the extracellular matrix (ECM) [3]. Indeed, FAK was long considered only as the central transducer of extracellular signaling, the most important triggered by integrins or growth factors, through its association with several proteins located in close proximity to the focal contacts. Over the last ten years, in addition to this kinase-dependent function, an unexpected kinase-independent role in the scaffolding and regulation of gene transcription was also discovered for FAK (ref. [4] and reviewed in [5][6]).

2. FAK Inhibitors

The critical and important role of FAK in the cancer progression of a plethora of human tumors [7][8][9][10] led to the development of selective FAK-targeting small molecules.

FAK inhibitors can be divided into three different categories: (i) kinase domain inhibitors, (ii) allosteric inhibitors and (iii) proteolysis-targeting chimera (PROTACs).

(i) Among the kinase domain inhibitors, the ATP-competitive ones are the most investigated FAK inhibitors. The ATP-competitive molecules bind to the FAK–kinase domain, directly competing with ATP, thus, inhibiting FAK signal transduction activity and the activation of several FAK downstream pathways (reviewed in [11][12]). Being able to selectively bind to the FAK ATP-binding domain, they are considered the most promising molecules to be translated and applied in clinical practice. Indeed, all the compounds inhibiting FAK that have accessed clinical trials and are currently under evaluation in Phase I and II belong to this category [12] (**Table 1**). One of the major challenges in the development of FAK inhibitors is to achieve a high selectivity towards proline-rich tyrosine kinase 2 (PYK2), another member of the FAK family. PYK2 is a tissue-specific non-receptor tyrosine kinase encoded by the protein tyrosin kinase 2 beta (PTK2B) gene (on Chr. 8p21.2), sharing 78% homology with FAK at the ATP binding site and a similar multi-domain organization [13][14]. Additionally, PYK2 regulates FAs formation and has been shown upregulated during FAK signaling suppression, thus, compensating for the loss of FAK, potentially promoting resistance [15][16]. Moreover, similarly to FAK, PYK2 can translocate from the cytoplasm to the nucleus thanks to its inability to associate with talin, which reduces its localization on FAs [17]. Additional similarities have been demonstrated between FAK and PYK2 in the nucleus, where, also, PYK2 can form complexes with p53 and MDM2, promoting p53 degradation in normal and cancer cells [17], and it can bind MDB2 [18]. However, differently from FAK, PYK2 has a unique characteristic, translocating to the nucleus in response to Ca++ signals in neurons [19]. Overall, the differences between PYK2's and FAK's nuclear functions, and their importance in FAK' signaling and inhibition, still remain to be clarified.

Table 1. Summary of FAK inhibitors in clinical trials.

Drug (Code Name), Trade Name	Target (IC50)	Clinical Trial Studies (a, b)	No. of Clinical Trials (a)	Phase (a)
GSK2256098 (GTPL7939)	FAK (0.4 nM)	adenocarcinoma, adult healthy subject, intracranial and recurrent meningioma mesothelioma, pancreatic cancer, pulmonary arterial hypertension, solid cancer	6; 4 completed, 2 active	Phase I: 4 Phase II: 2
VS-4718 (PND-1186)	FAK (1.5 nM)	relapsed or refractory AML, relapsed or refractory B-Cell ALL, metastatic cancer, non-hematologic cancers, pancreatic cancer	3; 2 terminated, 1 withdrawn	Phase I: 3
Defactinib (PF04554878, VS-6063)	FAK (0.6 nM) Pyk2 (0.6 nM)	advanced solid cancer, lung cancer, relapsed malignant and pleural mesothelioma, non-hematologic cancers, NSCLC, ovarian cancer, pancreatic cancer, PDAC	21; 4 terminated, 6 completed 10 active 1 withdrawn	Phase I: 9 Phase I/II: 2 Phase II: 10
VS-6062 (PF00562271)	FAK (1.5	head and neck cancer, pancreatic cancer, prostatic cancer	1; 1 completed	Phase I: 1

Drug (Code Name), Trade Name	Target (IC50)	Clinical Trial Studies (a, b)	No. of Clinical Trials (a)	Phase (a)
	nM) Pyk2 (14 nM)			
CEP-37440	FAK (2.3 nM) ALK (120 nM)	advanced or metastatic solid tumors	1; 1 completed	Phase I: 1
BI-853520 (IN10018)	FAK	colorectal cancer, metastatic melanoma, metastatic non hematologic malignancies, soft tissue sarcoma, stomach cancer [20][21][22][23]	3; 2 completed, 1 active	Phase I: 3

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conformation of the kinase domain, hampering interactions with receptor tyrosine kinases (RTKs) or auto-phosphorylation at Tyr397.

(a) From www.clinicaltrials.gov (accessed 18 October 2021); (b) AML—acute myeloid leukemia; ALL—acute lymphocytic leukemia; NSCLC—non-small-cell lung carcinoma; PDAC—pancreatic ductal adenocarcinoma.

Among the allosteric inhibitors are also those compounds that bind to non-kinase domains of FAK, such as FERM and FAT, acting on the scaffolding functions of the kinase by interrupting or avoiding protein–protein interactions (PPIs) between FAK domains and their associated proteins. FAK-MDM2, FAK-p53 and FAK-VEGFR3 PPIs have been intensely studied and specific allosteric compounds were discovered (reviewed in [24]).

(iii) PROTACs are new-generation compounds developed in the last years as inducers of protein degradation (ref. [25] and reviewed in [26]). PROTACs are heterobifunctional molecules able to hijack the ubiquitin–proteasome system (UPS) to degrade specific target proteins by concomitantly binding an E3 ubiquitin ligase, among which Von Hippel Lindau (VHL) or Cereblon (CRBN), and the selected protein. Conversely to traditional small molecules, PROTACs can target “undruggable” proteins lacking relevant binding sites but having pockets with small affinity for compounds that can be designed or found by screening, such as transcription factors or nuclear proteins. PROTACs against kinases have been developed and tested in pre-clinical settings [27][28]. Notably, one of the major benefits of PROTACs is their selectivity due to the specific interaction between the E3 ligase and the protein target.

Recently, a number of PROTACs against FAK that include a binder for the VHL E3 ligase have been developed [29][30][31]. PROTAC-3 was developed based on the ATP-competitive FAK inhibitor Defactinib (**Table 1**) fusing to the E3 ubiquitin ligase VHL, and has been shown to be more effective in inhibiting the activation of FAK and FAK-dependent cell migration and invasion in breast cancer cells in vitro [29]. FC-11 is a FAK PROTAC molecule obtained by the fusion of the VS-6062 ATP-competitive inhibitor (**Table 1**) with the E3 ubiquitin ligase CRBN. In vivo experiments showed FAK degradation in reproductive mouse tissues associated with a more than 90% reduction of total and phosphorylated (Tyr397) protein levels [30]. Very recently, the GSK215 FAK PROTAC has been developed from the ATP-competitive FAK inhibitor VS-4718 (**Table 1**) [31]. The efficiency of GSK215 was testified to by the marked reduction of FAK levels in liver tissues, in vivo. This pharmacologic study clearly shows

that FAK inhibition and FAK degradation have different effects, since GSK215 inhibited in vitro cell motility and 3D growth while VS-4718 was unable to do so.

3. FAK Inhibitors in Clinical Trials

In **Table 1** the authors summarize FAK inhibitors that are being evaluated in clinical trials as single agents or in combination. Of note, all the clinical trials using FAK inhibitors are focused on adult patients.

GSK2256098 (GTPL7939) is a potent, highly selective and reversible ATP-competitive FAK inhibitor (dissociation constant (Ki) = 0.4 nM). GSK2256098 inhibits FAK Y397 phosphorylation in several cancer cells. The drug treatment affects AKT and ERK downstream pathways, thus, impairing cell viability and anchorage -independent growth and inducing caspase-mediated apoptosis in L3.6P1 pancreatic ductal adenocarcinoma cells [32]. HepG2 HCC cells treated with GSK2256098 decreased phosphorylation levels of PI3K, AKT, STAT3 and JNK correlated with an anti-proliferative effect [33]. Preclinical data showed that GSK2256098 treatment reduces microvessel density and cellular proliferation and induces apoptosis more efficiently in PTEN-mutated than in PTEN wt uterine cancer cells [34]. Glioblastoma cells were found to be among the most sensitive to GSK2256098 in a screening of 95 cancer cell lines [35]. In agreement, in vivo experiments demonstrated that, in a human glioblastoma xenografted model, GSK2256098 treatment induced a time- and dose-dependent inhibition of FAK by reducing its phosphorylation [35]. To date, GSK2256098 is under investigation in six clinical trials, of which four are in Phase I (completed) and two in Phase II (one recruiting and one active but not recruiting) (**Table 1**). Two Phase I studies have enrolled healthy volunteers to evaluate and determine safety and biodistribution of GSK2256098 (NCT00996671, NCT02551653). A Phase I study, in the United Kingdom, on 62 patients with advanced solid tumors showed encouraging results on the acceptable safety profile and activity of GSK2256098 in mesothelioma patients (NCT01138033) [36]. A Phase Ib trial of GSK2256098 in combination with trametinib, a MEK/MAPK inhibitor, was conducted on 34 patients (of which 21 had malignant mesothelioma). Results here suggested that co-administration with GSK2256098 increases the trametinib uptake (NCT01938443) [37]. Moreover, two Phase II clinical trials have been activated to evaluate: (1) GSK225098 in combination with trametinib in advanced pancreatic cancer (NCT02428270; active, not recruiting) and (2) GSK225098 in combination with vismodegib, a hedgehog inhibitor, in intracranial and recurrent meningioma (NCT02523014; recruiting).

VS-4718 (PND-1186) is a potent, reversible and selective FAK inhibitor (Ki = 1.5 nM). VS-4718 IC50 dose reduced FAK Y397 phosphorylation in breast carcinoma cells, leading to tumor growth arrest and apoptosis induction [38]. A panel of 47 human cancer cell lines were tested for sensitivity to VS-4718, among which were renal cancer, thyroid cancer, ovarian cancer, breast carcinoma, melanoma, mesothelioma and non-small-cell lung cancer cell lines [39]. Overall, data from this study suggested that the absence of the Merlin tumor suppressor correlates with high sensitivity to VS-4718 treatment in malignant pleural mesothelioma in vitro and in vivo. VS-4718 showed potent inhibition activity in vitro in a pediatric preclinical testing program (PPTP) and excellent tolerance in vivo [40]. Moreover, VS-4718 can act as a competitive substrate for ABCB1 and ABCB2, thus affecting the activity of these transporters and leading to the intracellular accumulation and increased efficacy of small molecules [41]. Recently, transcriptomic analysis performed on a uveal melanoma cell line treated with VS-4718 revealed that the treatment

downregulates genes stimulated by KRAS, EGFR and cytokines, such as IL-21 and IL-15. VS-4718 repressed also the expression of genes downregulated by JAK2, p53 and BMI. Interestingly the authors observed a down-regulation of YAP signature genes due to a strong reduction of YAP nuclear localization after VS-4718 treatment [42]. In a preclinical study unrelated to cancer, VS-4718 was used to inhibit FAK in proliferating vascular smooth cells (vsmc) to show that inactive FAK enters to the nucleus where it forms a complex with Skp2, an E3-ubiquitin ligase, and CDH1, an activator for APC/C E3 ligase complex, to promote their degradation [43]. The results were the increase of the two cyclin-dependent kinase inhibitors, p21 and p27, and the consequent blockade of vsmc proliferation [43]. VS-4718 was investigated in three Phase I clinical trials (**Table 1**) but all of them were either terminated with no available results (NCT01849744, NCT02651727) or withdrawn (NCT02215629).

Defactinib (PF04554878, VS-6063) is a potent dual and reversible ATP-competitive inhibitor of FAK and PYK2 (Ki = 0.6 nM, both) [44][45]. Preclinical studies revealed that Defactinib reduced FAK Y397 phosphorylation in a dose-dependent manner, and combinatorial treatment with paclitaxel, a chemotherapy drug, reduced cell proliferation and induced apoptosis in ovarian cancer cells [46]. Moreover, Defactinib can overcome the in vitro paclitaxel-resistance mediated by the DNA- and RNA-binding proteins YB-1 [46]. Defactinib induces dissociation of PI3K from FAK in esophageal squamous cell carcinoma, thus resulting in impaired AKT signaling and in the transcriptional downregulation of several oncogenes such as SOX2, MYC, EGFR, MET, MDM2 and TGFBR2, thus reducing tumor growth and metastatic ability [47]. Human malignant mesothelioma (MM) cells overexpressing calreticulin, a Ca2+-binding protein critical for MM cell survival in vitro, show increased nuclear FAK and resistance to Defactinib in vitro [48]. The co-treatment with Defactinib and docetaxel, another chemotherapy drug, impaired the proliferation of castration-resistant prostate cancer cells in vitro and in vivo [49]. Defactinib is under evaluation in 21 clinical trials: 9 in Phase I (2 terminated, 5 completed, 1 recruiting and 1 withdrawn), 2 in Phase I/II (both recruiting) and 10 in Phase II (2 terminated, 1 completed, 6 recruiting and 1 active but not recruiting) (**Table 1**). Phase I studies established the acceptable safety, tolerability, pharmacokinetics profile and clinical activity in 9 patients (NCT01943292) [45] and 46 patients with advanced solid tumors (mostly colorectal, ovarian or pancreatic cancer) (NCT00787033) [50]. In the Phase II trial NCT01951690, Defactinib monotherapy showed modest clinical activity in heavily pretreated KRAS mutant non-small cell lung carcinoma (NSCLC) patients [51]. A Phase II study, involving 344 patients affected by malignant pleural mesothelioma, demonstrated that Defactinib treatment after first line chemotherapy did not improve either progression-free survival (PFS) or overall survival (OS) (NCT01870609) [52].

VS-6062 (PF00562271) is a potent dual and reversible ATP-competitive inhibitor of FAK and PYK2 (Ki = 1.5 nM and Ki = 14 nM, respectively) [53]. VS-6062 potently reduces FAK Y397 phosphorylation in epidermal squamous cell carcinoma [53] and Ewing sarcoma cell lines [54], resulting in the repression of downstream pathways. Preclinical studies demonstrated that co-treatment with VS-6062 and Sunitinib, a multi-targeted RTK inhibitor (RTKi), strongly inhibits angiogenesis and proliferation in liver and epithelial ovarian cancers [55][56]. Furthermore, VS-6062 treatment impairs T cell proliferation, adhesion to ICAM-1 (intercellular adhesion molecule-1) and interactions with antigen-presenting cells [57]. VS-6062 treatment reduced FAK activation and consequently SRC and BCAR1 phosphorylation, inhibiting cell growth and inducing apoptosis in liposarcoma cells [58]. VS-6062 was evaluated in a Phase I clinical trial (**Table 1**) in which 99 patients with advanced solid tumors were enrolled.

Results from the trial showed a safety profile of VS-6062 and a time-dose dependent non-linear absorption, distribution, bioavailability, metabolism and excretion (NCT00666926; completed) [59].

CEP-37440 is a potent dual and reversible ATP-competitive inhibitor of FAK and ALK (Ki = 2.3 nM and Ki = 120 nM, respectively). In vitro treatment with CEP-37440 reduced the cell proliferation of anaplastic large-cell lymphoma cells [60]. CEP-37440 was able to completely inhibit the proliferation of FC-IBC02 breast cancer cells in vitro, affecting the transcriptional expression of genes related to apoptosis, interferon signaling and cytokines such as IFI27, IFI6, IFI35, IRF7, CCL5, IL32, IL23A, OAS2, OAS3, OAS1, MX1, ISG15, BIK and KDR [61]. Furthermore, CEP-37440 showed efficacy in breast cancer preclinical models both in vitro and in vivo [61]. It also exhibited good oral ADME (absorption, distribution, metabolism and excretion) properties, high bioavailability in several animal species (mouse, rat and monkey) and excellent activities in in vivo models of ALK- and FAK-positive tumors [60][61]. Furthermore, CEP-37440 is a brain-penetrant drug [62]. CEP-37440 was evaluated and successfully completed Phase I clinical trials (**Table 1**). Thirty-two patients with advanced or metastatic solid tumors were enrolled to determine the maximum tolerated dose (MTD), safety and tolerability of oral CEP-37440 (NCT01922752), but the results are not available.

BI-853520 is a selective and potent FAK inhibitor that binds the FAK kinase region, blocking ATP access [44]. It inhibits FAK Y397 phosphorylation in prostate cancer cell lines with an IC50 of 1 nM [63]. Furthermore, it has been demonstrated that it reduces tumorsphere formation and in vivo orthotopic malignant pleural mesothelioma growth [64]. In addition, recent studies reported that BI-853520 has high specificity for FAK in breast cancer cells [65]. Indeed, it represses FAK activity through the inhibition of Y397 autophosphorylation, while in FAK's homologue PYK2 phosphorylation was unaffected [65]. RNA-seq analysis performed on BI-853520-treated 4T1 breast cancer cells xenografted in mice revealed the downregulation of genes involved in proliferation and cell cycle progression, such as CDK1 and CDK4, and the upregulation of genes involved in T-cell differentiation and proliferation, cytokine production and leukocyte activation [65]. Currently, BI-853520 effects are under investigations in three different Phase I clinical trials, of which two are completed (NCT01905111, NCT01335269) and one is recruiting (NCT04109456). NCT01905111 clinical trial assessed the safety, tolerability, MTD and preliminary data on antitumor effects of BI-853520 monotherapy in a cohort of 21 Taiwanese and Japanese patients affected by various advanced or metastatic tumors. The results showed that BI-853520 has an acceptable safety profile and potential antitumor effects [66]. BI-853520 MTD and antitumor efficacy was assessed also in a Phase I clinical trial on 96 patients affected by advanced and metastatic non-hematologic tumors (NCT01335269). The trial was completed and showed that BI 853520 has an acceptable safety profile and modest antitumor activity at a MTD of 200 mg in the selected patients' cohort [67]. Finally, a recruiting, Phase Ib clinical trial (NCT04109456) is aimed to investigate safety, tolerability, pharmacokinetics and anti-tumor effects in metastatic melanoma patients.

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