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Endothelial FAK as a Therapeutic Target in Disease

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Abstract

Focal adhesions (FA) are important mediators of endothelial cytoskeletal interactions with the extracellular matrix (ECM) via transmembrane receptors, integrins and integrin-associated intracellular proteins. This communication is essential for a variety of cell processes including EC barrier regulation and is mediated by the non-receptor protein tyrosine kinase, focal adhesion kinase (FAK). As FA mediate the basic response of EC to a variety of stimuli and FAK is essential to these responses, the idea of targeting EC FAK as a therapeutic strategy for an assortment of diseases is highly promising. In particular, inhibition of FAK could prove beneficial in a variety of cancers via effects on EC proliferation and angiogenesis, in acute lung injury (ALI) via the attenuation of lung vascular permeability, and in rheumatoid arthritis via reductions in synovial angiogenesis. In addition, there are potential therapeutic benefits of FAK inhibition in cardiovascular disease and diabetic nephropathy as well. Several drugs that target EC FAK are now in existence and include agents currently under investigation in preclinical models as well as drugs that are readily available such as the sphingolipid analog FTY720 and statins. As the role of EC FAK in the pathogenesis of a variety of diseases continues to be explored and new insights are revealed, drug targeting of FAK will continue to be an important area of investigation and may ultimately lead to highly novel and effective strategies to treat these diseases.

Introduction

Focal adhesions (FA) are intercellular complexes through which the endothelial cytoskeleton interacts with the extracellular matrix (ECM) via transmembrane receptors, integrins and integrin-associated intracellular proteins. FA act as a molecular bridge between the cell and extracellular matrix that sense and respond to an array of stimuli, allowing precise communication between the ECM and cytoskeleton. This communication is essential for cell growth, cell shape changes, cell migration, differentiation, and tailoring of the extracellular environment as well as EC barrier regulation (Romer et al., 2006). Focal adhesion kinase (FAK), a non-receptor protein tyrosine kinase, is the primary enzyme involved in the engagement of integrins and assembly of FA through the catalyzing of several downstream signals and is regulated primarily through Src mediated tyrosine phosphorylation (Clark et al., 1998; Yuan, 2002). In addition, EC FAK has other intracellular signaling properties independent of its regulation of FA. Given the essential role FA in the basic response of endothelial cells (EC) to a variety of stimuli and the

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importance of FAK in this context, the idea of targeting FAK as a therapeutic strategy for diseases involving the vasculature is a promising one and is the topic of this review. We will first consider the role of FAK in various diseases, with particular focus on the endothelium, and then consider the therapeutic potential of strategies targeting endothelial FAK with specific drugs including statins.

Role of Endothelial FAK in Disease

A potential role for endothelial FAK in the pathophysiology of a variety of diseases can be appreciated by first recognizing the role of FAK in normal endothelial physiology. In particular, FAK is a key mediator of angiogenesis during development evidenced by the early embryonic lethality of mice engineered to harbor an endothelial-specific deletion of FAK (Shen et al., 2005). Increased endothelial apoptosis and increased vascular permeability has been identified as an important mechanism underlying lethality in these embryos (Zhao et al., 2010).

FAK is also a multi-functional signaling molecule beyond its ability to regulate FA turnover. For example, upon association with adherens junctions, FAK phosphorylation (Tyr-397 and Tyr-576) regulates RhoA signaling via p190RhoGAP (Holinstat et al., 2006; Chang et al., 2009). Separately, FAK Tyr-925 phosphorylation has been found to regulate MAPK signaling via Grb2 (Schlaepfer and Hunter, 1996). These variable effects are dependent, in part, on FAK localization and specific sites of FAK tyrosine phosphorylation.

In light of its central role in normal endothelial physiology and its pleiotropic signaling properties intracellularly, it should come as no surprise that FAK has been identified as a key pathogenic mediator of a variety of diseases. The most widely studied disease in this regard is cancer as the role of FAK in cancer-related angiogenesis is now well recognized and aberrant FAK activation may promote tumor angiogenesis. The pathogenic role of endothelial FAK in cancer has been less well characterized but mounting evidence supports its functional role in tumor progression and infiltration. Beyond this, however, endothelial FAK has been implicated as an important determinant of vascular inflammation in rheumatoid arthritis and vascular permeability in acute lung injury (ALI) and may play a role in the pathogenesis of diabetic nephropathy and cardiovascular disease as well (Table 1).

Cancer

The link between FAK and cancer is supported by evidence of increased FAK expression in several different cancers including laryngeal, esophageal, colon, breast, and prostate as well as malignant melanoma (Aronsohn et al., 2003; Kahana et al., 2002; Miyazaki et al., 2003; Owens et al., 1995; Tremblay et al., 1996). In addition, the functional role of endothelial FAK in cancer has been the focus of a number of investigations. For example, evidence that tumor angiogenesis is mediated by endothelial FAK is provided by reduced tumor growth in mice with an inducible endothelial FAK deletion that have been injected with either melanoma or lung carcinoma cells (Tavora et al., 2010). These same animals demonstrate decreased angiogenic responses to vascular endothelial growth factor (VEGF). Moreover, FAK-deleted lung EC isolated from these mice exhibit attenuated VEGF-induced Akt phosphorylation, decreased proliferation, and increased apoptosis (Tavora et al., 2010).

Endothelial FAK has also been implicated as an essential mediator of the proliferation and tissue infiltration of gliomas as tumor vessels in conditional endothelial-specific FAK knockout mice demonstrate reduced permeability which is associated with attenuated tumor growth compared to wildtype animals (Lee et al., 2010). Additionally, tumor vessels in these knockout mice were found to have restored cell-cell junction proteins compared to those of

wildtype animals. In separate studies, inhibition of glioma cell-mediated angiogenesis by human umbilical cord blood stem cells was associated with downregulation of FAK (Dasari et al., 2010). Collectively, these studies and others strongly implicate EC FAK in the regulation of tumor growth and invasion via augmented endothelial proliferation and tumor neoangiogenesis.

Rheumatoid Arthritis

A key feature of the pathogenesis of rheumatoid arthritis (RA) is vascular inflammation characterized by augmented angiogenesis, the formation of new vessels from pre-existing vessels, as well as defective endothelial precursor function and de novo vascular formation or vasculogenesis (Szekanecz et al., 2010). Synovial angiogenesis contributes to pannus formation and serves to propagate localized inflammation via increased access of inflammatory cells to the synovium (Kimball and Gross, 1991; Paleolog, 1997). The angiogenic response is regulated to a large degree by endothelial integrin $\beta 3$ (Brooks et al., 1994) which is upregulated in the synovial vasculature of patients with RA (Johnson et al., 1993). Integrin $\beta 3$, in turn, associates with FAK thus implicating FAK as a potential therapeutic target in RA (Guan, 1997; Schaller et al., 1995). In support of this, strategies aimed specifically at inhibiting integrin $\beta 3$ have now shown significant promise in various rodent models of RA (Badger et al., 2001; Storgard et al., 1999; Zhou et al., 2009) and suggest alternative strategies aimed directly at FAK may also be worth investigation.

Acute Lung Injury (ALI)

ALI is a challenging clinical problem encountered in the intensive care unit and is associated with significant morbidity and mortality. A cardinal feature of ALI is an increase in lung vascular permeability precipitated by an exuberant inflammatory response with subsequent lung EC barrier disruption. Evidence suggests that EC responses to mechanical and inflammatory stimuli in ALI are mediated by FA as site-specific phosphorylation and specific interactions of FA proteins have been functionally linked to changes in EC barrier function (Shikata et al., 2003a; Shikata et al., 2003b; Sun et al., 2009). At the center of these events is FAK which modulates differential regulation of the Rho GTPases, Rho and Rac, via phosphorylation of the FA adaptor protein, paxillin (Birukova et al., 2009). These effects are characteristic of EC signaling induced by VEGF and hepatocyte growth factor, both of which are elevated in ALI (Mura et al., 2004; Yanagita et al., 1993). In addition, excessive mechanical stretch of lung EC, known to precipitate ALI, induces increased FAK aggregation with integrin $\alpha_v\beta_3$ consistent with increased focal adhesion formation and associated with increased tyrosine phosphorylation of paxillin (Bhattacharya et al., 2003). In turn, phosphorylation of paxillin is associated with increased expression of P-selectin, a pro-inflammatory mediator, which co-localizes with paxillin.

Further evidence for an important role of FAK in the pathogenesis of ALI is provided by FAK regulation of EC barrier disruption induced by reactive oxygen species (ROS) (Usatyuk and Natarajan, 2005) as activation of NADPH oxidase with subsequent generation of ROS has been identified as an important mediator of injury in ALI (Gao et al., 2002; Sato et al., 2002). For example, EC treated with hydrogen peroxide (H_2O_2) exhibit increased permeability in association with increases in both FAK expression (Yang et al., 2004) and Tyr-397 phosphorylation of FAK (Usatyuk and Natarajan, 2005). H_2O_2 -induced EC barrier disruption, however, is attenuated in cells transfected with a FAK-related non-kinase. In these same cells, downstream effects of FAK activation are also attenuated including phosphorylation of both β -catenin and paxillin (Usatyuk and Natarajan, 2005). These findings suggest that increased vascular permeability characteristic of ALI could be attenuated by specific strategies aimed at inhibiting FAK. It should be noted, however, that the role of FAK in endothelial permeability is not fully established and, in fact, there is

evidence that reductions in FAK expression are associated with augmented agonist-induced EC barrier disruption and prolonged barrier recovery *in vitro* (Mehta et al., 2002). Accordingly, it may be the case that the therapeutic potential of FAK inhibition in ALI may ultimately be dependent on the degree of inhibition or perhaps the timing of the strategy employed.

Diabetic Nephropathy

Diabetic nephropathy is a common manifestation of microvascular disease in patients with diabetes and a pathologic feature is glomerular sclerosis characterized by hyaline deposits in the glomerular arterioles. The role of endothelial FAK in diabetic nephropathy has only recently been investigated. Interestingly, in rats subjected to hyperglycemia, renal glomeruli exhibit increased tyrosine phosphorylation of EC FAK in association with increased expression of integrin $\beta 1$ although total FAK expression is unchanged (Regoli and Bendayan, 1999). Notably, these events occur prior to appreciable changes in the renal extracellular matrix suggesting that FAK may play an important role in the pathogenesis of diabetic nephropathy. While further exploration of the role of FAK in diabetic nephropathy is warranted, these findings suggest FAK may be a useful therapeutic target in patients at risk for diabetic nephropathy.

Cardiovascular Disease

Evidence for an important protective role for endothelial FAK in atherosclerotic heart disease is largely indirect but highly suggestive nonetheless. It is well recognized that high shear stress associated with laminar blood flow across the endothelium is atheroprotective, while endothelial responses to turbulent blood flow and low shear stress, as occurs at vascular branch points, are known to be atherogenic (Hahn and Schwartz, 2009; Malek et al., 1999; Traub and Berk, 1998). Further, EC subjected to high shear stress exhibit increased recruitment of FAK to FA in association with increased FAK activation (Li et al., 1997) while inhibition of phosphorylated FAK via a phospho-specific antibody (Tyr397) attenuates flow-induced vasodilation mediated by endothelial nitric oxide (Koshida et al., 2005). This data support FAK as an important determinant of EC responses to shear stress and suggest a potentially significant pathogenic role for FAK in atherosclerotic heart disease. However, this is an area of investigation that remains to be fully explored.

Drug Targeting of FAK

Several drugs that either directly or indirectly affect endothelial FAK are now in existence (Table 2). Many of these have only been studied in preclinical models yet seem to hold therapeutic promise. Others, such as the sphingolipid analog FTY-720, have been more thoroughly studied and are currently available for specific indications in limited patient populations. Perhaps the most intriguing drugs known to target FAK, however, are the statins, a class of drugs that are readily available, affordable, and relatively safe. It is likely that drug targeting of FAK will be an important area of investigation as we continue to learn more about the role of FAK in the pathogenesis of disease.

Statins

The statins, a class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG)-CoA reductase inhibitors and the most widely prescribed class of drugs in the world, are commonly used for their potent lipid lowering properties and beneficial effects on the morbidity and mortality associated with coronary artery disease. However, there is a growing body of evidence that the beneficial effects of statins extend beyond their ability to lower serum cholesterol levels and these drugs are now recognized to have direct effects on endothelial signaling, including

effects on FAK. Accordingly, a strong case can be made that they warrant consideration as a novel strategy for treatment of a variety of diseases known to be mediated by FAK.

Inhibition of HMG-CoA reductase by statins prevents prenylation of HMG-CoA, a post-translational modification that results in either farnesylation or geranylgeranylation, the addition of a 15-carbon side chain or two 20-carbon side chains, respectively. A downstream product of farnesylation is cholesterol while geranylgeranylation is requisite for membrane anchoring and subsequent activation of the Rho family GTPases, including RhoA (Goldstein and Brown, 1990; Zhang and Casey, 1996). In turn, RhoA activation at the membrane is required for FAK activation (Clark et al., 1998). Accordingly, statins would be predicted to inhibit EC FAK. Indeed, statin inhibition of FAK is evidenced by decreased tyrosine phosphorylation of FAK in basic fibroblast growth factor (bFGF)-stimulated EC after prolonged pre-treatment with cerivastatin (12–24 hours) (Vincent et al., 2002). These findings are also associated with decreased phosphorylation of Akt, a downstream target of FAK.

Statin effects on FAK have been linked to effects on integrins which are dependent on FAK for signal regulation (Clark et al., 1998). In particular, statin treatment attenuates FAK activation and expression of integrin $\beta 1$ in squamous carcinoma cells (Takeda et al., 2007) while statins attenuate both FAK and integrin $\beta 1$ activation in human leukemic cells but without effects on integrin $\beta 1$ expression levels (Kawakami et al., 2002). However, statin-treated EC are characterized by a marked upregulation of integrin $\beta 4$ (Jacobson et al., 2004). Notably, inhibition of EC integrin $\beta 4$ is associated with augmented mitogen-activated protein kinase (MAPK) signaling and increased phosphorylation of the protein tyrosine phosphatase, SHP-2 (Chen et al., 2010). SHP-2 in turn is known to regulate tyrosine dephosphorylation of FAK (Manes et al., 1999; Qi et al., 1999). Evidence of the functional link between integrin $\beta 4$ and FAK in EC is provided by increased phosphorylation of FAK in integrin $\beta 4$ -silenced EC and in preliminary studies we have recently confirmed the inhibition of FAK phosphorylation (Tyr-576) associated with statin treatment (Figure 1). While these events remain to be fully characterized our current understanding is consistent with the upregulation of integrin $\beta 4$ in statin-treated EC that results in FAK inhibition, despite the concomitant inhibition of SHP-2, and the attenuation of downstream events including MAPK activation (Figure 2).

The therapeutic potential of statins on the basis of their ability to inhibit FAK is now supported by numerous reports of protective effects of these drugs in animal models of ALI (Jacobson et al., 2005; Muller et al.), inflammatory arthritis (Haruna et al., 2007; Leung et al., 2003) and diabetic nephropathy (Giunti et al., 2010; Yao et al., 2010). Moreover, there is data from relevant patient populations that these effects may be clinically significant including evidence of a protective effect of statins in patients at risk for ALI (Mortensen et al., 2008; Schlienger et al., 2007), decreased incidence of rheumatoid arthritis associated with statin use (Chodick et al., 2010), and a renal-protective effect of statins in patients with diabetic nephropathy (Lam et al., 1995; Tonolo et al., 1997). The effect of statins on the incidence of cancer has also been studied and while the data is mixed (Dale et al., 2006; Kuoppala et al., 2008), there is some evidence that the incidence of specific types of cancer may be reduced in patients treated with a statin including stomach, liver, and colorectal cancers (Kuoppala et al., 2008; Poynter et al., 2005). Finally, while the beneficial effect of statins in patients with cardiovascular disease are well recognized (Scandinavian Simvastatin Survival Study, 1994; Shepherd et al., 1995), there is evidence that these benefits may not be entirely attributable to their lipid-lowering effects. This is suggested by recent data indicating that newer classes of cholesterol-reducing medications fail to produce the same clinical benefits in patients with hypercholesterolemia despite their comparable potency reducing serum cholesterol levels (Barter et al., 2007; Brousseau et al., 2004).

FTY720

FTY720 is a synthetic analog of the bioactive phospholipid, sphingosine 1-phosphate (S1P) which is found in platelets and erythrocytes and induces EC barrier enhancement both *in vitro* (Garcia et al., 2001) and *in vivo* (McVerry et al., 2004; Peng et al., 2004). EC signaling initiated by S1P involves receptor ligation with subsequent site-specific tyrosine phosphorylation of FAK (Tyr-576) via Gi signaling and phospholipase C activation (Lee et al., 2000). This is followed by FA rearrangement with redistribution to the cell periphery and EC barrier enhancement (Shikata et al., 2003b). Notably, differential site-specific tyrosine phosphorylation of FAK is known to occur in response to either barrier-protective or barrier-disruptive agonists (Shikata et al., 2003a). While FTY720 has been studied for use in patients with multiple sclerosis due to its immunosuppressive effects (Brinkmann et al., 2010), this drug has recently demonstrated protective effects in animal models of ALI (Camp et al., 2009; Liu et al., 2008). Although further studies are needed these findings suggest that FTY720 may also be useful in other diseases in which FAK is a pathogenic mediator.

SKI-606

SKI-606, also known as bosutinib, is a dual Src/Abl kinase inhibitor which inhibits signaling molecules downstream of Src including FAK, proline-rich tyrosine kinase 2 (Pyk2) and Crk-associated substrate (p130^{Cas}). SKI-606 has been shown to attenuate motility and invasion of breast cancer cells *in vitro* (Vultur et al., 2008). These effects are associated with an inhibition of phosphorylation of FAK at Tyr-576, Tyr-577 and Tyr-925, Src-dependent phosphorylation sites, while FAK expression levels are not altered. Although this drug has recently shown promise *in vivo* in a phase II trial of select patients with breast cancer (Campone et al., 2011), its effects on EC are not well characterized. However, at least one report has identified EC barrier protection conferred by SKI-606 (Gorbunova et al., 2011) suggesting that this agent may be useful in other clinical contexts.

Inhibitors of Integrin $\beta 3$: Tumstatin and Etaracizumab

While not a direct FAK inhibitor, tumstatin is a fragment of type IV collagen that has both anti-angiogenic and pro-apoptotic properties which has been studied for its ability to inhibit tumor growth in various mouse models (Maeshima et al., 2000; Maeshima et al., 2001). This molecule binds to integrin $\beta 3$ which is expressed in a variety of cell types including tumor cells and normal endothelial cells (Ruegg et al., 1998) and, like other integrins, is dependent on FAK for intercellular signaling (Vuori, 1998). Indeed, tumstatin has been shown to inhibit EC FAK signaling (Maeshima et al., 2002). Similarly, etaracizumab is a monoclonal antibody against integrin $\beta 3$ which has been investigated as a potential therapy in a variety of cancers and shown early promise (Kim et al., 2009; Moschos et al., 2010; Veeravagu et al., 2008). In a phase 0 study of patients with metastatic melanoma treatment with etaracizumab was associated with decreased tyrosine phosphorylation of FAK in isolated melanoma cells and endothelial cells (Moschos et al., 2010). Accordingly, the clinical potential for both tumstatin and etaracizumab may extend well beyond cancer therapy. Moreover, antibodies directed against other integrins are currently under investigation as novel cancer therapies (Li et al., 2010; Mita et al. 2010). These agents may similarly demonstrate effects on FAK that could lead to their consideration in other clinical contexts.

Direct FAK Inhibitors

Several ATP-competitive small molecule inhibitors of FAK have been identified including the bis-amino pyrimidine inhibitors, PF-562,271 and PF-573,228, and the bis-anilino pyrimidine inhibitors, TAE226, TAF089, TAF672, and AZW592. The chemical structures of these molecules are shown in Table 2. The crystal structures of these molecules, both

alone and in complex with FAK, has been published elsewhere (Roberts et al., 2008; Lietha et al., 2008). To date, these agents have been studied largely for their potential role in cancer treatment. For example, TAE226 has been investigated in several preclinical studies and was found to attenuate tumor angiogenesis (Sakurama et al., 2009; Schultze et al., 2010). These effects are associated with inhibition of FAK in both tumor cells and in normal EC. Similarly, PF-562,271 has demonstrated potent FAK inhibition *in vivo* (Roberts et al., 2008). PF-562,271 is now being studied in a phase I clinical trial and early indications are that it has a tolerable safety profile (Bolos et al., 2010). Should the results of early clinical studies of these agents continue to be encouraging these drugs will undoubtedly warrant investigation in other FAK-mediated diseases as well.

Conclusion

The role of FAK in the pathogenesis of disease is an area of ongoing investigation. However, there is now clear evidence that endothelial FAK is an important mediator of a number clinical conditions that are either characterized by derangements in vascular function (ALI, cardiovascular disease) or are dependent on the vasculature for full elaboration of disease (cancer, RA). While drug targeting of FAK has shown early promise in several different cancers, specific targeting of EC FAK in cancer and other diseases has gone largely unstudied. Nonetheless, a number of agents are now available that target EC FAK signaling and preliminary findings in cell and animal models as well as observational data from relevant patient populations suggest that they may represent novel and effective therapeutic options in a variety of FAK-mediated diseases. While caution is certainly warranted in the study of these agents given the importance of FAK in normal endothelial physiology and the potential for adverse effects associated with excessive FAK inhibition, this is certainly an area of investigation that will continue to be explored and may ultimately lead to a profound change both in how these diseases are managed by clinicians and in patient outcomes.

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Figure 1. Inhibition of EC FAK by statins is mediated by integrin β 4

(A) Immunofluorescent images are shown from human pulmonary EC grown on collagen and then transfected with either silencing RNA specific for integrin β 4 (siITGB4), a molecule markedly upregulated in EC by statins, or a non-specific RNA (nsRNA) as a control. Inhibition of integrin β 4 is associated with a significant increase in tyrosine phosphorylation of FAK that co-localizes with cortical actin (arrows) consistent with a strong regulatory role for integrin β 4 in EC FAK signaling. (B) Western blots of human pulmonary artery EC pretreated with simvastatin (5 mM, 16 h) followed by vehicle or thrombin (1 U/ml, 10 min) indicate decreased phosphorylation of FAK (Tyr 576) compared to controls (* $p < 0.05$, $n = 3$ /experimental condition).

Figure 2. Endothelial signaling by statins

Statin effects on EC are diverse but include the marked upregulation of integrin $\beta 4$. Statin upregulation of integrin $\beta 4$ inhibits both FAK and SHP-2, a protein tyrosine phosphatase that has previously been linked to the dephosphorylation of FAK. These effects are associated with statin attenuation of MAPK signaling with downstream attenuation of the expression of inflammatory cytokines such as IL-6 and IL-8.

Table 1

Potential role of endothelial FAK in disease.

Disease	Role of Endothelial FAK in Pathophysiology	References
Cancer	augmented endothelial proliferation and tumor neoangiogenesis	Tavora et al., 2010 Lee et al., 2010 Dasari et al., 2010
Rheumatoid Arthritis	increased synovial angiogenesis mediated via integrin $\beta 3$	Brooks et al., 1994 Johnson et al., 1993 Guan, 1997
Acute Lung Injury	EC barrier disruption via differential Rho GTPase signaling	Birukova et al., 2009 Bhattacharya et al., 2003 Usatyuk and Natarajan, 2005
Diabetic Nephropathy	increased integrin $\beta 1$ expression and alterations in renal extracellular matrix	Regoli and Bendayan, 1999
Cardiovascular Disease	increased atherogenesis in response to shear stress	Li et al., 1997 Koshida et al., 2005

Table 2

Properties of various FAK inhibitors.

Drug	Direct or Indirect FAK inhibition	Mechanism of action	IC50 of FAK inhibition <i>in vitro</i>	Other known targets (IC50)	Chemical structure of direct inhibitors	References
Statins	indirect	inhibition of HMG CoA-reductase	unknown			Vincent et al., 2002 Jacobson et al., 2004
FTY720	indirect	S1P receptor ligation	unknown			Lee et al., 2000 Mandala et al., 2002
SKI-606	indirect	Src kinase inhibition	300 nM	Abl kinase		Vultur et al., 2008
Tunstatin	indirect	Inhibition of integrin $\beta 3$	unknown			Maeshima et al., 2002
Etaracizumab	indirect		unknown			Moschos et al., 2010
PF-562,271	direct	ATP-competitive, reversible inhibition	1.5 nM	Pyk2 (14 nM)		Roberts et al., 2008
PF-573,228	direct		4 nM	Pyk2 (1 μ M)		Slack-Davis et al., 2007
TAE 226	direct	ATP-competitive, reversible inhibition	5.5–6.24 nM	Pyk2 (5.5 nM), IGF-IR (~140 nM)		Liu et al., 2007 Liebha et al., 2008

Drug	Direct or Indirect FAK inhibition	Mechanism of action	IC50 of FAK inhibition <i>in vitro</i>	Other known targets (IC50)	Chemical structure of direct inhibitors	References
TAF089	direct		7.7 nM			Liettha et al., 2008
TAF672	direct		unknown (likely similar to TAF089)			Liettha et al., 2008
AZW592	direct		17.76 nM			Liettha et al., 2008