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The role of FAK in tumor metabolism and therapy

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Abstract

Focal adhesion kinase (FAK) plays a vital role in tumor cell proliferation, survival and migration. Altered metabolic pathways fuel rapid tumor growth by accelerating glucose, lipid and glutamine processing. Besides the mitogenic effects of FAK, evidence is accumulating supporting the association between hyper-activated FAK and aberrant metabolism in tumorigenesis. FAK can promote glucose consumption, lipogenesis, and glutamine dependency to promote cancer cell proliferation, motility, and survival. Clinical studies demonstrate that FAK-related alterations of tumor metabolism are associated with increased risk of developing solid tumors. Since FAK contributes to the malignant phenotype, small molecule inhibition of FAK-stimulated bioenergetic and biosynthetic processes can provide a novel approach for therapeutic intervention in tumor growth and invasion.

Keywords

Focal adhesion kinase; glucose; lipogenesis; glutamine; solid tumor; proliferation; motility; molecular targeting; small molecule inhibition

1. Introduction

Cell attachment to the extracellular matrix (ECM) is involved in fundamental activities from embryogenesis to tumorigenesis. Actin filaments are fastened to focal adhesions with the help of a multi-protein complex that “adheres” actin microfibers to the ECM proteins. Numerous proteins located in the focal adhesions or actin filament termini-ECM joint regions have been identified such as α-actinin, filamin, vinculin, fibronectin, integrin, talin, paxillin, and focal adhesion kinase (FAK). Focal adhesions are dynamic structures that

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Conflict of Interest

The authors declare that there are no conflicts of interest.

constantly change or reorganize in response to microenvironmental cues such as ECM alterations, growth factors, and nutrient availability (Fletcher & Mullins, 2010). For example, integrin engagement or growth factor stimulation promotes FAK interaction with Src, leading to activation of downstream pathways such as Ras/MAPK signaling (Guan & Shalloway, 1992; Schlaepfer, Hanks, Hunter, & van der Geer, 1994). FAK interactions with integrins and growth factor receptors contribute to cell anchorage dependency, motility, and invasive growth, which are associated with malignant overgrowth and pro-survival.

Human FAK, encoded by the protein tyrosine kinase 2 gene, consists of N-terminal FERM, central catalytic, and c-terminal focal adhesion targeting (FAT) domains. The N- and C-terminal domains of FAK form an autoinhibitory structure (Lietha, et al., 2007). FAK interactions with membrane receptors including integrins and IGF1R are believed to induce a conformational switch of FAK to expose phosphorylation sites such as Y397. Phosphorylation of FAK at Y397 can promote FAK binding and phosphorylation of acceptor proteins including Src. FAK activation of Src can stimulate several signal transduction pathways such as PI3K-Akt, RAF/JNK, and Rho/Rac/PAK (J. Zhang, et al., 2013). Activation of those cascades modulates cell motility and survival. For example, Y397 phosphorylation of FAK plays a critical role in cell migration (Ritt, Guan, & Sivaramakrishnan, 2013). Casapse cleavage of FAK into two fragments results in removal of autoinhibition and release of the FAT domain (Gervais, Thornberry, Ruffolo, Nicholson, & Roy, 1998). The FAT fragment inhibits FAK activity through dephosphorylation and induces cell death.

Overexpression and hyperphosphorylation of FAK are associated with many types of solid tumors. Lethality of FAK knock out indicates an essential role of FAK in fetal development. In adult tissues, FAK levels are relatively low, but can be elevated during wound healing and transformation processes (Gates, King, Hanks, & Nanney, 1994; Moissoglu & Gelman, 2003; Nagaharu, et al., 2011; Tamura, et al., 2003). Hyperactivity of FAK can promote survival and motility, contributing to tumorigenicity and metastasis. For example, the levels of FAK expression were low in the normal colon or benign breast epithelium but high in the biopsies derived from patients with colon and metastatic breast cancer (Cance, et al., 2000; Lark, et al., 2005). Furthermore, the levels of FAK mRNA in normal tissues were very low, but were overexpressed in varied primary and metastatic tumors (Golubovskaya, Kweh, & Cance, 2009). FAK overexpression and phosphorylation were associated with Barrett's associated esophageal adenocarcinoma, prostate-carcinoma, gastric cancer recurrence, squamous cell carcinoma, progression of hepatocellular carcinoma, thyroid cancer, small-cell lung carcinoma, and oral tumor cell invasion (Aprikian, Tremblay, Han, & Chevalier, 1997; Aronsohn, Brown, Hauptman, & Kornberg, 2003; Itoh, et al., 2004; S. J. Kim, et al., 2004; Lai, et al., 2010; Ocak, Chen, Callison, Gonzalez, & Massion, 2012; Rovin, Frierson, Ledinh, Parsons, & Adams, 2002; Schneider, et al., 2002; Watanabe, et al., 2008; Yuan, et al., 2010).

The mitogenic effects of FAK on cell proliferation and survival in normal and neoplastic tissues have been well accepted and reviewed (Hauck, Hsia, & Schlaepfer, 2002; Lietha, et al., 2007; G. Liu, et al., 2008; Schlaepfer, et al., 1994; Ucar & Hochwald, 2010; Zachary & Rozengurt, 1992). The role of FAK in metabolism under normal and disease conditions such

as cancer has not been critically evaluated or summarized. Increasing evidence indicates a role for FAK modulation of glucose, lipid and glutamine metabolism that is likely essential for tumor cell rapid growth, survival and invasion.

2. FAK-promoted glucose consumption in neoplastic proliferation

Growth factors such as insulin/IGF-1 and anchorage are primary extracellular cues that stimulate cell proliferation. FAK interactions with IGF-1R and integrins transmit these growth signals by activating effectors such as PI3K/Akt, promoting glucose consumption to fuel rapid growth in tumor cells (Fig 1).

i) FAK modulation of insulin-stimulated glucose uptake

The direct binding of FAK with insulin receptor substrate (IRS) proteins and the role of FAK in controlling expression of insulin receptor substrate-1 (IRS-1) has been previously shown (Lebrun, Baron, Hauck, Schlaepfer, & Van Obberghen, 2000). Insulin binds to its receptors, triggering IRS-FAK activation and intracellular signal cascades that mediate a number of cellular processes including an increase in glucose transport (Baron, Calleja, Ferrari, Alengrin, & Van Obberghen, 1998; El Annabi, Gautier, & Baron, 2001; Goel & Dey, 2002; Huang, Cheung, Parsons, & Bryer-Ash, 2002; Knight, Yamauchi, & Pessin, 1995; Lebrun, et al., 2000; Ouwens, et al., 1996; Pillay, Sasaoka, & Olefsky, 1995). FAK activation reorganizes actin filaments to form a mesh harboring the glucose transporter. Translocation and activation of transporter 4 promotes glucose uptake through PI3K/Akt activation in skeletal muscle cells (Bisht & Dey, 2008). Furthermore, fibronectin activation of FAK through integrin-ECM interaction stimulates glucose uptake in endothelial cells (Paik, Ko, Jung, & Lee, 2009). In hepatocytes, FAK modulates glycogen synthesis by stimulating Akt/GSK-3β signaling (Huang, et al., 2002).

Oncogenes alter metabolic pathways, contributing to increased glucose uptake and dependency for cancer cell viability. This unique feature of malignant cells has been applied to tumor detection using positron emission tomography imaging with the radiolabeled glucose analog ^{18}F-fluorodeoxyglucose. High levels of glucose increase integrin-ECM stimulation of FAK activity and enhances stem cell proliferation (Kroder, et al., 1996). On the other hand, glucose withdrawal induces aberrant tyrosine phosphorylation of focal adhesion protein in glucosedependent cell lines such as glioblastoma, sarcoma, and melanoma (Graham, et al., 2012). FAK modulation of insulin signaling is likely to be cell type specific since FAK activation is negatively correlated with glucose uptake in neuronal cells (Gupta, Bisht, & Dey, 2012).

Glucose is one of the major cellular sources of energy and building materials that are required for proliferation. FAK stimulation of glucose uptake is expected to be correlated with increased proliferation. Indeed, FAK overexpression or hyperactivation is common in solid tumors. In addition, tyrosine kinases including FAK modulate the levels of glucose transporters (Anichini, et al., 1997; Bisht & Dey, 2008) and the proliferation index (T. J. Liu, et al., 2007; Serrels, et al., 2012; Zhelev, et al., 2004) in muscle and tumor cells.

ii) FAK-IGF1R signaling in tumor glucose metabolism

IGF-1/IGF1R signaling has potent effects on cell survival through promoting proliferation and suppressing apoptosis. The metabolic effects of the IGF-1/IGF1R axis on glucose metabolism are less known. Several lines of observations support the role of the IGF-1/IGF1R cascades in glucose processing. First, IGF1R often forms complexes with insulin receptors. Thus, IGF1R can have influence on insulin stimulation of glucose consumption via the insulin receptor/IGF1R complex. Secondly, IGF-1 can directly bind with insulin receptors, indicating IGF signaling in modulation of glucose metabolism. Thirdly, IGF-1/IGF1R stimulation of rapid proliferation needs sustained energy and cellular biosynthesis. IGF1R stimulated glucose uptake can meet this high demand (Kuemmerle, 2012).

Activation of IGF-1R signaling is correlated with primary and metastatic malignancies such as prostate, breast, pancreatic, and lung cancer (Moser, et al., 2008; Putz, et al., 1999; Resnik, Reichart, Huey, Webster, & Seely, 1998; Warshamana-Greene, et al., 2005). The anti-apoptosis property of IGF1R-triggered kinase cascades contributes to cancer cell resistance to cytotoxicity and vascularization. When EGFR pathways are blocked by inhibitors such as Erlotinib, IGF1R can resume EGFR-related signaling and promote breast cancer survival. IGF1R-enhanced angiogenesis is involved in tumor invasion and metastasis (Ackermann, Morse, Delventhal, Carvajal, & Konerding, 2012; Kucab & Dunn, 2003; Menu, et al., 2007).

The Hochwald laboratory and others have demonstrated FAK interaction with and stabilization of IGF1R (Andersson, D'Arcy, Larsson, & Sehat, 2009; W. Liu, et al., 2008). The N-terminal FERM domain of FAK directly binds to IGF1R, leading to PI3K/Akt activation and survival. Small molecule inhibition of FAK-IGF1R interactions induces apoptosis and prevents tumor growth. Antibody-mediated inhibition of IGF1R signaling results in decreased Akt activity and glucose uptake (Shang, et al., 2008). Impaired kinase-independent biological functions of IGF1R leads to decreased intracellular glucose levels and viability of cells derived from human embryonic kidney and metastatic breast cancer (Janku, Huang, Angelo, & Kurzrock, 2013).

iii) Clinical associations of increased glucose levels and cancer risk

Increased glucose uptake and associated metabolism are hallmarks of malignancy. Abnormal IGF1R signaling can contribute to tumor metabolic pathways since increased IGF1R mass and/or activity may enhance insulin receptor-induced glucose utilization. IGF1R signaling may promote the shift of cellular balance favoring biosynthesis to support neoplastic proliferation. Several studies show that high glucose levels are correlated with increased cancer risk (Chocarro-Calvo, Garcia-Martinez, Ardila-Gonzalez, De la Vieja, & Garcia-Jimenez, 2013; Kabat, et al., 2012; Wulaningsih, et al., 2013). A large clinical study (540,309 participants) demonstrated that high serum glucose levels were linked with increased risks of development of colon cancer (Wulaningsih, et al., 2012). Quartile analysis indicated a positive association between glucose levels and risks of kidney cancer (Van Hemelrijck, et al., 2012). These observations demonstrate the possible need for monitoring aberrant glucose levels or metabolism to identify individuals at high risk of developing certain types of malignancies such as colon cancer (Aleksandrova, et al., 2011).

3. Lipid-FAK interactions in tumorigenesis

i) The role of lipids in FAK-promoted tumor motility and invasive growth

Lipid metabolism can affect the scaffolding and kinase functions of FAK (Fig 2). Lipids in the cell membrane provide the necessary microenvironment for FAK interactions with receptors such as integrins and IGF1R. In addition, lipid rafts can facilitate the translocation of FAK-associated complexes in FAK-promoted signal transduction. For example, lipid rafts are associated with FAK stimulation of ERK1/2 and neurite outgrowth (Niethammer, et al., 2002). Lipid rafts and FAK interactions contribute to cell adhesion signaling (Shima, Nada, & Okada, 2003).

FAK activation and association with Src family members can transmit growth cues by forming complexes with membrane-bound receptors such as integrins, IGF1R, and EGFR in lipid rafts. Indeed, translocation of the neuronal cell adhesion molecule from FGFR complexes into FAK-associated lipid rafts promotes focal adhesion assembly, cell motility and invasive growth (Lehembre, et al., 2008). Disrupting the lipid rafts attenuates EMT and cell spreading (Lehembre, et al., 2008). A synthetic lipid analog promotes invasiveness of colon cancer cells through upregulation of integrin-FAK phosphorylation/activation, interactions, and scaffolds (Van Slambrouck, et al., 2007).

ii) FAK and lipid metabolism in neoplastic growth

FAK can affect lipid metabolism by controlling the supply of precursors and enzyme activity of proteins involved in lipid synthesis. Citrate is exported from mitochondria into the cytosol and converted to fatty acid (Fig 2). Growth factor and anchorage-dependent activation of FAK enhances glucose uptake. This can maintain the carbon supply for increased lipid synthesis in proliferative cells.

FAK and fatty acid biosynthesis: Citrate conversion to acetyl-CoA, malonyl-CoA, long chain fatty acid, and unsaturated fatty acid oleate involves ACLY, acetyl-CoA carboxylase, fatty acid synthetase, and stearoyl-CoA desaturase (Fig 2). Aberrant enzyme activity and *de novo* lipogenesis are associated with many types of solid tumors such as lung, gastric, and breast cancers (Migita, et al., 2008; Varis, et al., 2002; Yancy, et al., 2007). SREBP-1 activation of PI3K/Akt signaling and Myc-regulated glutaminolysis to lipid metabolism are linked to metabolic reprogramming in cancer cells (Guo, Bell, Mischel, & Chakravarti, 2013). Inhibition of key lipogenic enzymes, ACLY and fatty acid synthetase, decreases FAK, Akt, and paxillin activity and cell motility (Zaytseva, et al., 2012). Insulin activation of ACLY involves FAK-induced phosphorylation/translocation of insulin receptors (Brownsey, Edgell, Hopkirk, & Denton, 1984). Depletion of raft cholesterol impairs chemokine and growth factor stimulated FAK recruitment and adhesion, thus, contributing to anoikis like apoptosis (J. H. Jeon, et al., 2010; Le, Honczarenko, Glodek, Ho, & Silberstein, 2005; E. K. Park, et al., 2009; Ramprasad, et al., 2007).

iii) Lipids and cancer risk

Cancer and proliferating cells have enhanced biosynthesis of fatty acids by channeling glucose and/or glutamine into the TCA cycle and upregulation of lipid biosynthetic enzymes

(Ridgway, 2013). The levels of certain lipid components and lipogenic enzymes are associated with the risks of kidney and breast cancer (Van Hemelrijck, et al., 2012; Wang, et al., 2013). High fat diets stimulate bile acid secretion into the gastrointestinal tract. Bile acids are correlated with colon cancer, and lipid-lowering drugs may reduce the risk of colorectal tumor (Cai, Dupertuis, & Pichard, 2012; McMichael & Potter, 1985; Simon, et al., 2012; van Duijnhoven, et al., 2011). At high physiological levels, the bile acid deoxycholic acid, induced colonic tumor formation in mice (Bernstein, et al., 2011). Deoxycholic acids decreased phosphorylation of FAK at tyrosine-576/577 (Tyr-576/577) and Tyr-925, promoted Src binding with FAK, and triggered inside-out signaling in colon cancer cells (Khare, Holgren, & Samarel, 2006). FAK interactions with Src can induce downstream cascades including PI3K/Akt. Indeed, bile acid-induced colon cancer is likely associated with PI3K/Akt signaling-increased survival and proliferation (Raufman, Shant, Guo, Roy, & Cheng, 2008).

4. FAK-associated deregulation of glutamine metabolism in cancer cell survival and proliferation

Many cancer cells such as pancreatic ductal adenocarcinoma rely on glutamine for their survival and biosynthetic needs (Wilson, Erickson, Antonyak, & Cerione, 2013). Although the direct link of FAK activation and glutamine deregulation warrants further investigation, current data suggests that the scaffold and kinase functions of FAK can contribute to cell sensing microenvironmental cues and modulation of amino acid and protein metabolism. For example, FAK activation is associated with K-Ras and H-Ras induced transformation of NIH3T3 cells and rat fibroblasts (J. Jeon, et al., 2007). In addition, aberrant activation of oncogenes such as Myc and K-Ras mediate reprograming of glutamine metabolism (Son, et al., 2013; Wise & Thompson, 2010) (Fig 3). FAK hyper-activation is associated with uncontrolled cancer survival and proliferation. Targeting malignancy-specific glutamine consumption provides an unique approach to attack solid tumors.

i) FAK and glutamine dependency for tumor growth and invasion

Proliferating cells consume glutamine to fuel the tricarboxylic acid cycle and provide nitrogen for nucleotide, nonessential amino acid and hexosamine biosynthesis (Fig 3). Cancer cells often develop dependency on specific amino acids (Fu, et al., 2003). For example, deprivation of tyrosine and phenylalanine in the medium induces apoptosis of melanoma cells through FAK-related signaling pathways (Fu, Yu, Pelayo, Ferrans, & Meadows, 1999). Glutamine metabolism is dramatically increased in Her2-type breast cancer (S. Kim, Kim do, Jung, & Koo, 2013). Oncogene K-Ras modulation of glutamine metabolism is essential for pancreatic cancer cell survival and growth (Son, et al., 2013). FAK interactions with Her2 promote tumorigenesis (Lark, et al., 2005; Vartanian, Goodearl, Lefebvre, Park, & Fischbach, 2000). Furthermore, micrometastatic cells express activated/phosphorylated FAK, Her2 and PI3K, suggesting the roles of Her2-FAK/Src-PI3K activation in malignant and invasive growth (Kallergi, Mavroudis, Georgoulias, & Stournaras, 2007; Vadlamudi, Sahin, Adam, Wang, & Kumar, 2003).

ii) The association of FAK activation and glutamine-modulated autophagy in cancer cell survival

Autophagy is a key strategy for cell survival under stress conditions such as nutrient deficiency. Degradation of non-essential and/or redundant cellular compartments leads to release of building blocks to fuel key energy and biosynthetic processes. Cancer cells can capture this machinery to retain their pro-survival and proliferative states. For instance, pancreatic cancer cells have elevated levels of autophagy, and suppression of autophagy prevents proliferation and tumor growth. FAK stimulates PI3K/Akt signaling; whereas PI3K/Akt activation increases the levels of glutamine and its synthetase (van der Vos, et al., 2012). Increased glutamine production promotes autophagy, survival and proliferation (Ko, et al., 2011; W. M. Liu, et al., 2013; Nicklin, et al., 2009; Sakiyama, Musch, Ropeleski, Tsubouchi, & Chang, 2009). These observations support the notion that growth factor stimulation of FAK-PI3K-Akt signaling contributes to cell survival and proliferation through upregulation of glutamine synthetase and autophagy.

iii) FAK modulation of glutamine metabolism in stress-resistant neoplastic cells

Rapid cell proliferation demands energy and building blocks. High levels of energy generation and biosynthesis are correlated with production of byproducts such as oxidants. In order to cope with excessive oxidants, FAK-overexpressing solid tumors must upregulate signaling pathways that promote antioxidant production. Growth factor-FAK-PI3K/Akt signaling resulting in increased glutamine synthetase and glutamine levels can serve as anti-oxidative machinery. Son et al., observed that glutamine deprivation suppresses pancreatic ductal tumor cell growth through a non-canonical pathway of glutamine consumption that is involved in serial conversion of glutamine-oxaloacetate-malate-pyruvate (Son, et al., 2013). This process leads to increased NADPH/NADP+ ratios, which has anti-oxidative activity. Antioxidants, GSH and N-acetylcysteine, abolish glutamine deficiency-suppressed cancer cell growth (Son, et al., 2013), suggesting that cancer cells use glutamine metabolism to maintain cellular redox balance. Glutamine has been reported to modulate cell protection against oxidative stress in intestinal epithelial cells (Musch, Hayden, Sugi, Straus, & Chang, 1998). Glutamine supplements attenuate 2,4,6-trinitrobenzene sulfonic acid-induced oxidative stress in a rat model of colitis (Crespo, et al., 2012). Increased flux of glutamine toward glutathione synthesis reduces oxidative stress in flies and human cell lines (Nicolay, et al., 2013). A direct link of FAK modulation of glutamine metabolism in neoplastic cells has not been shown at this time.

iv) The link between aberrant glutamine metabolism and tumorigenesis

Excessive glutamine consumption contributes to malignant survival, genomic instability, and unscheduled proliferation (Fernandez-Marcos & Serrano, 2013; Jeong, et al., 2013). Use of small molecules targeting glutamine metabolism allows linkage of the Rho GTPases and NF-κB to mitochondrial glutaminase hyper-activity in cancer cells (Wilson, et al., 2013). Abnormalities in glutamine metabolism has been linked to pancreatic, lung, and breast cancer, which is associated with oncogenes such as K-Ras, solute-linked carrier family A1 member 5 and Myc (Dang, 2013; Hassanein, et al., 2013; S. Kim, et al., 2013; Son, et al., 2013).

The role of FAK in glutamine deregulation-associated tumorigenesis include 1) activating glutamine metabolism-related oncogenes such as K-Ras, 2) relaying signals from oncogenes to glutamine metabolic enzymes, and 3) direct regulation of glutamine metabolism. FAK levels are often elevated in solid tumors. siRNA inhibition of FAK expression attenuates EGF and fibronectin-stimulated overexpression of oncogenes and cell cycle regulatory proteins, resulting in decreased cell migration and proliferation (J. H. Park & Han, 2009; J. H. Park, Ryu, & Han, 2011). Phosphorylation of FAK at tyrosine 407 negatively regulates FAK activity. Decreased Y407 phosphorylation is correlated with Ras transformation of fibroblasts, indicating that FAK activation stimulates Ras signaling (J. Jeon, et al., 2007; Wade, Brimer, Lyons, & Vande Pol, 2011). On the other hand, R-Ras promotes FAK signaling, and synergizes with alpha2beta1 integrin stimulation of FAK activation (Kwong, Wozniak, Collins, Wilson, & Keely, 2003). Furthermore, Myc activates FAK in neuroblastoma cells (Beierle, et al., 2007). Glutamine restriction inhibits FAK activity and impairs melanoma attachment and spreading, suggesting the involvement of FAK in glutamine metabolism-modulated malignant cell anchorage and motility (Fu, et al., 2004).

5. Targeting FAK-mediated metabolic signaling pathways

The interplay among glycolytic/mitochondrial glucose processes, lipid biosynthesis, and nucleotide/protein/antioxidant metabolism are dynamically balanced in response to a constantly changing microenvironment. FAK overexpression and hyperactivation can promote glucose metabolism to fuel cell proliferation in cancer cells (Fig 4). Targeting FAK activation and its interactions with proteins that are involved in glucose, fatty acid, and glutamine metabolism can be an attractive approach to combat tumor growth and metastasis. Inhibitors targeting FAK function, FAK binding with IGF1R, FAK-activated key lipogenic enzymes and glutamine synthetase have been developed (Vander Heiden, 2011). The NIH clinical trial database (clinicalTrial.gov) and PubMed have been searched to identify inhibitors targeting FAK activity and its metabolic pathways.

i) FAK inhibitors

VS-6063 and VS-4718 are drug candidates, developed by Verastem, for FAK inhibition targeting cancer stem cells. A phase I/Ib clinical trial has been conducted with Paclitaxel in combination with the company's first FAK inhibitor, defactinib or VS-6063, in subjects with advanced ovarian cancer. Verastem reports that VS-6063 was granted orphan drug status by the US FDA and European regulators for mesothelioma, an asbestos-related rare lung cancer with limited treatment options. Verastem also reports that VS-6063 was well tolerated at the dose of 400 mg BID in combination with weekly Paclitaxel. Previously, pre-clinical studies indicated that VS-6063 (formerly PF-04554878) reduced cancer stem cells, primary tumor mass and metastasis (Schultze & Fiedler, 2011). A recently completed Phase I clinical study shows that the FAK inhibitor, PF-00562271, is tolerated at a dose of 125 mg BID in patients with pancreatic, head and neck, prostatic **n**eoplasms (Infante, et al., 2012).

VS-4718 is the second compound, developed by Verastem, currently under study in a Phase I clinical trial evaluating patients with metastatic non-hematologic malignancies.

GSK2256098 is a small molecule inhibitor of FAK developed by GlaxoSmithKline. A phase I clinical trial dose escalation study in subjects with solid tumors known to express FAK has been performed. Preliminary findings from the first trial of GSK2256098 in subjects with mesothelioma suggested that it had some effects on disease spread in patients lacking an active tumor suppressor gene, NF2 ((ECCO), 2012).

Numerous new FAK inhibitors have been designed, produced, and tested, including diarylamino-1,3,5-triazine, 1,3,4-oxadiazole, pyrazolo[4,3-c][2,1]benzothiazines derivatives, cFAK-C4 and Y15 (Dao, et al., 2013; Dunn, Heffler, & Golubovskaya, 2010; Ma, 2011; Schultze & Fiedler, 2010; Tomita, et al., 2013; S. Zhang, et al., 2013).

ii) Inhibitors targeting FAK activation of IR/IGF1R

Insulin and IGF-1 can stimulate FAK activity (Baron, et al., 1998); and FAK binds with and stabilizes IGF-1R. Therefore, FAK hyperactivity can promote insulin/IGF-1 signaling-mediated glucose metabolism in cancer cells. Blocking basic insulin signaling can cause serious metabolic disorders. Inhibitors targeting IGF1R have been developed in the attempt to attenuate tumor growth.

IGF1R inhibitors: Several companies are currently testing small molecule kinase inhibitors targeting the IGF1R tyrosine kinase and many have had limited utility (Hewish, Chau, & Cunningham, 2009; Pollak, 2008). Over 50 clinical trials of IGF1R inhibitors in patients with many types of tumors have been registered with NIH (Clinicaltrials.gov, August 2013). Inhibitor names, tumor types, trial stages and statuses are summarized in Table 1. Approaches targeting the ATP competitive binding site have limitations due to lack of specificity for IGF1R. This is due to sequence homology and identity, particularly in the kinase domain, and structural similarity of IGF1R to other receptor tyrosine kinases such as the insulin receptor. A similar argument can be made for kinase inhibitors of FAK. In addition, it appears that disruption of the kinase domain is not sufficient to specifically interfere with the downstream signaling of IGF1R (or FAK) and it is unclear whether the kinase function or the scaffolding function of these proteins is more important (Golubovskaya, et al., 2012; Su, et al., 2013).

Targeting FAK-IGF1R interaction represents a novel approach to inhibit abnormal hyperactivation of survival signaling. Both FAK and IGF-1R are upregulated and promote the malignant phenotype making them appropriate targets for developmental therapeutics. We have shown that dual inhibition of FAK and IGF1R leads to a synergistic increase in cell detachment and apoptosis (Hochwald, et al., 2009; W. Liu, et al., 2008; Zheng, et al., 2010). However, selective dual small molecule inhibitors of both proteins are not available or demonstrate toxicity (Golubovskaya, et al., 2008; Kurenova, et al., 2009; Watanabe, et al., 2008). Inhibitors targeting FAK protein binding with IGF1R offer significant promise to inhibit the function of both FAK and IGF-1R proteins and be more efficacious than existing IGF-1R inhibitors that have failed testing in clinical trials. These FAK inhibitors may be associated with low rates of side effects for the following reasons: 1) FAK-IGF1R signaling can primarily stimulate abnormal survival signaling. Specific inhibition of FAK FERM domain binding with IGF1R should have minimal effects on FAK binding with other

partners, indicating a limited impact on basic signaling. 2) FAK levels decrease after fetal development to very low levels in adult normal tissues; therefore, these inhibitors can have less impact on normal tissues.

Small organic molecules are particularly attractive as inhibitors of intracellular protein–protein interactions because of the ability to modify their structures to achieve optimal target binding, and because of their ease of delivery in *in vivo* systems. Several investigators have developed an approach for therapeutic intervention by targeting FAK-IGF1R protein-protein binding. Molecular docking, cell-based screening and xenograft mouse models have been used for the identification of lead compounds such as INT2–31 that inhibit FAK-IGF1R binding and tumor growth (Ucar, et al., 2012; Ucar, et al., 2013).

iii) Targeting ACLY and fatty acid synthetase

ACLY hyperactivation is a common feature of many tumors and is correlated with FAK overexpression. Inhibition of ACLY activity induces the arrest of cancer cell cycle progression in vitro and in vivo (Migita, et al., 2013; Zaidi, Swinnen, & Smans, 2012). ACLY deficiency exerts an anticancer effect via increased ROS and p-AMPK (Migita, et al., 2013). These observations support the notion that FAK-ACLY signaling contributes to increased lipogenesis in cancer cells, but potent and specific antagonists to inhibit abnormal constitutive activation of these proteins are lacking.

Normal cells rely on dietary fatty acids. Therefore, depletion of fatty acid synthetase has limited impact on normal cells. FAK and fatty acid synthetase are often highly upregulated in solid tumors. Furthermore, fatty acid synthetase is essential for cancer cell survival. Inhibition of fatty acid synthetase induces apoptosis. Inhibitors targeting fatty acid synthetase prevent cell proliferation and growth of prostate cancer (Chen, Chang, Chuang, Tai, & Hwang, 2012). Several potent inhibitors of fatty acid synthetase have been patented and are commercially available (Pandey, Liu, Xing, Fukuda, & Watabe, 2012). Since the levels of FAK and fatty acid synthetase in normal tissues are low or undetectable, clinical trials of fatty acid synthetase inhibitors in patients with tumors overexpressing FAK and/or fatty acid synthetase may result in the discovery of potent anti-cancer drugs with minimal side-effects. No trials evaluating fatty acid synthetase inhibitors in malignancy have been reported to date.

iv) Inhibition of aberrant glutamine metabolism

FAK can enhance the activities of oncogenes such as K-Ras and Myc; while their activation has been linked to increased glutamine synthetase activity. Derivatives of methionine sulfoximine, phosphorus containing analogues of glutamic acid, bisphosphonates and miscellaneous inhibitors targeting glutamine synthetase have been developed (Berlicki, 2008). A glutaminolytic drug, L-Asparaginase, and the glutamine synthetase inhibitor, methionine sulfoximine, depleted the glutamine pool, arrested cell cycle progression, and induced caspase-3 mediated apoptosis in human hepatocellular carcinoma cells (Tardito, et al., 2011). Oncogenic Myc promotes glutaminase expression and cancer cell addiction to glutamine (Wise, et al., 2008). Inhibition of glutaminase activity using siRNA or small molecule, BPTES [bis-2-(5 phenylacetamido-1, 2, 4-thiadiazol-2-yl) ethyl sulfide],

prevented growth and tumorigenesis (Lobo, et al., 2000; Thangavelu, et al., 2012). Glutaminase inhibitors attenuate cancer-related gene expression through histone and epigenome modification (Simpson, Tryndyak, Pogribna, Beland, & Pogribny, 2012). A cell-permeable benzophenanthridinone compound 968 inhibits mitochondria glutaminase, resulting in repressed growth and invasive activity in NIH3T3 cells expressing Dbl, Cdc42-F28L, Rac-F28L or RhoC-F30L mutants, in SKBR3 and in MDA-MB231 cancer cells. The observations suggest that the balance of glutamine and glutamate plays a vital role in tumor cell survival. Depletion of either glutamine or glutamate pools in the tumor cells can lead to oxidant production and apoptosis. Although preclinical results have shown the anticancer effects of targeting glutamine metabolisms, there is no clinical trial that is registered in the NIH clinical trial data base as of August, 2013.

6. Summary and prospective

FAK plays a key role in tumor metabolism that is characterized by excessive consumption of and addictive dependency on glucose, lipids and glutamine. Constitutive FAK binding with and stabilization of IR/IGF1R promotes effectors such as IRS and PI3K/Akt cascades, promoting glucose consumption to fuel rapid cell division and enhance survival.

Lipids are major components of cell membranes that are essential for excessive cell proliferation. The role of FAK in tumor lipid metabolism is less well studied. However, experimental evidence supports the notion that FAK can contribute to the malignant cell deregulation of lipid bioprocesses. First, FAK interactions with membrane receptors such as integrins, EGFR, and IGF1R to form complexes are critical for initiation of lipid biosynthesis. Second, FAK activation is correlated with overexpression of lipid enzymes. Finally, FAK-promoted glucose consumption can provide carbon sources for lipid synthesis.

Oncogene-induced glutamine consumption can fuel rapid cell growth and maintain redox balance in cancer cells. Constitutive FAK activation stimulates oncogenes such as K-Ras and Myc, which promotes the activities of glutamine metabolic enzymes including glutamine synthetase and glutaminase. Increased levels of cellular glutamine pools boost TCA-mediated metabolic pathways and antioxidant production, which is essential for rapid cell proliferation.

Defining and establishing the link between FAK-related pathways and abnormal metabolism can promote the design and development of new drugs for the treatment of cancer. For example, inhibitors targeting FAK modulation of IGF1R, ACLY, and glutaminase have been reported to attenuate abnormal glucose, fatty acid and glutamine consumption as well as tumorigenesis. However, clinical trials of those potent inhibitors in patients with tumors are lacking. It is expected that the development of new potent small molecules and further clinical studies of the known inhibitors targeting FAK and/or its downstream metabolic effectors can lead to the identification of novel compounds to kill cancer cells with minimal side-effects on normal tissues.

Abbreviations

FAK	focal adhesion kinase

FASN	Fatty Acid Synthase
IGF1R	insulin-like growth factor 1 receptor
ACLY	ATP citrate lyase
ECM	extracellular matrix
IRS	insulin receptor substrate
IR	insulin receptor
PBTES	Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide
GS	glutamine synthetase
GLUT	glucose transporter

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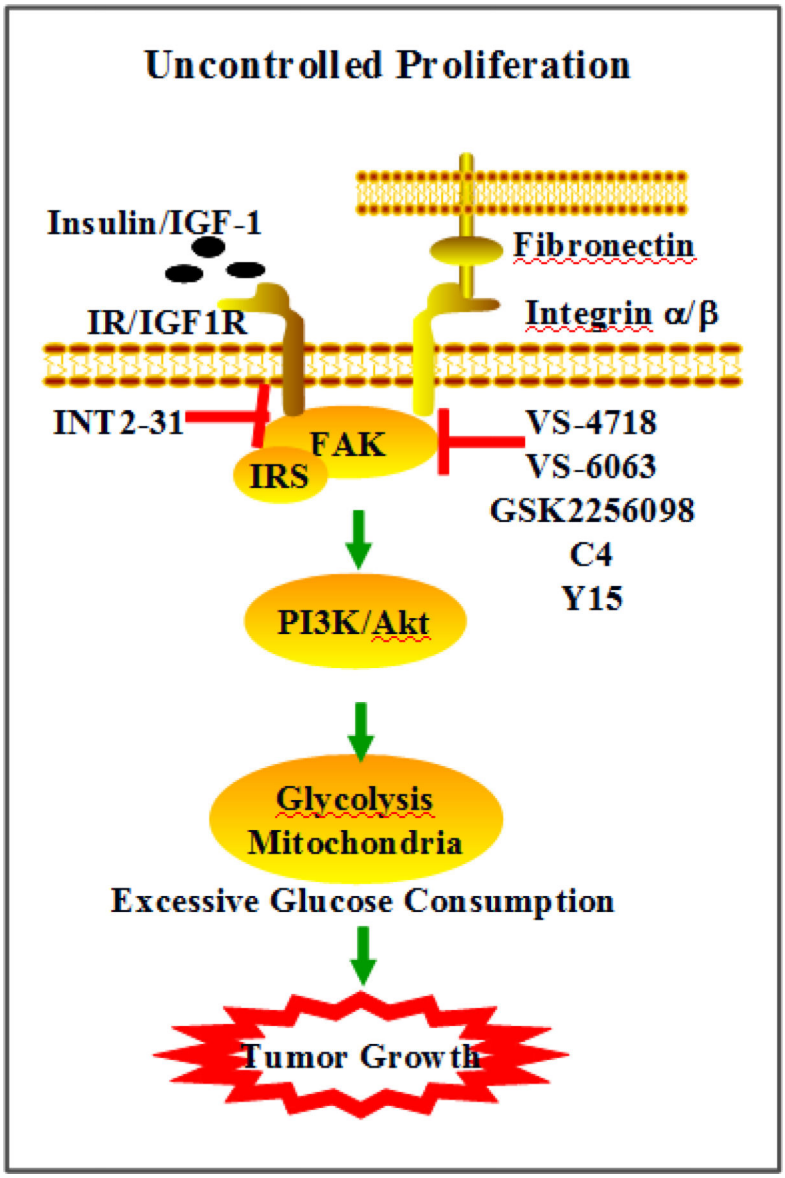

Fig 1. FAK modulation of cancer cell glucose consumption and proliferation.

Growth factors, insulin/IGF1R, and/or anchorage-activated integrin trigger FAK activation. Downstream factors, IRS and PI3K/Akt induce alteration of glycolysis and mitochondrial respiration. Excessive glucose consumption provides energy and precursors to rapidly growing cells. Inhibitors targeting FAK or FAK-IGF1R interactions can prevent malignant cell glucose consumption and growth.

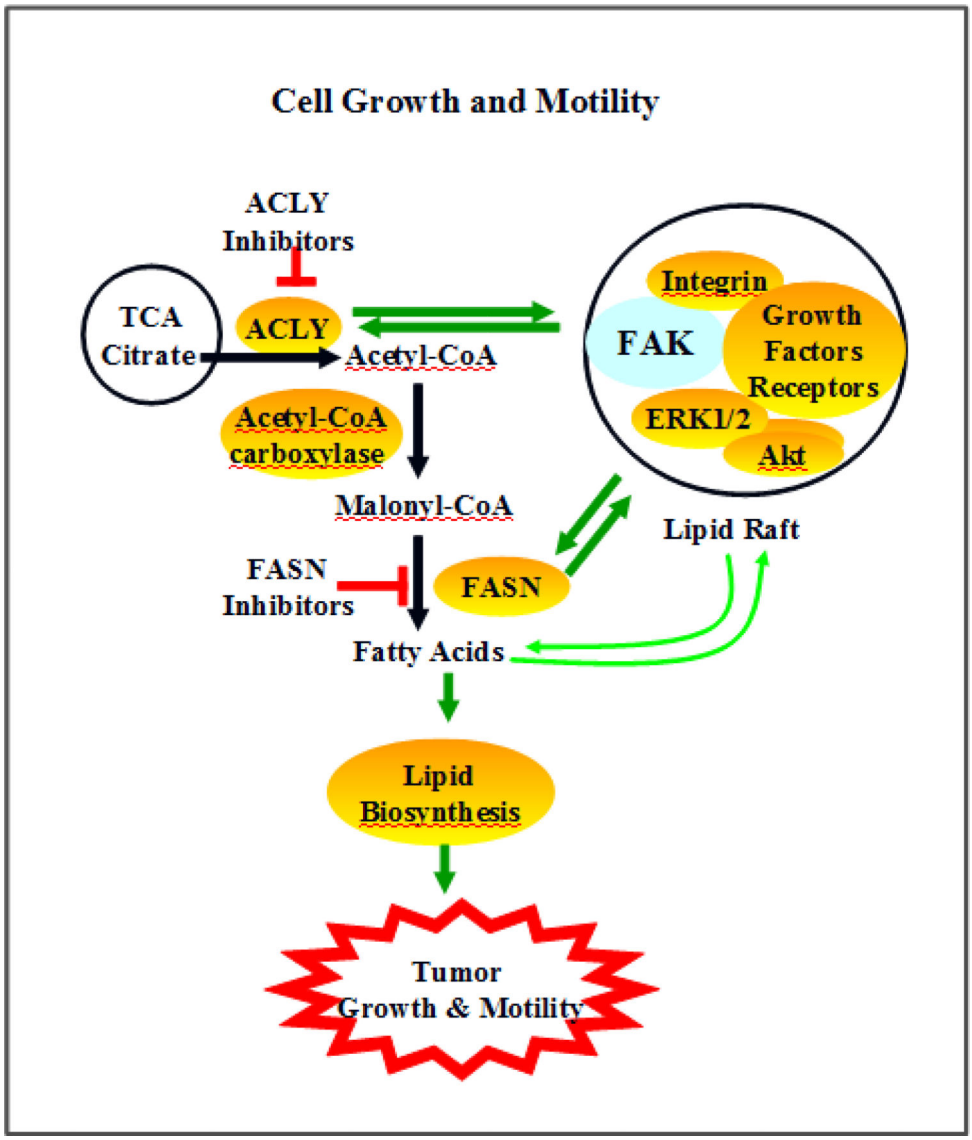

Fig 2. The roles of FAK in lipid-mediated tumor growth and invasion.

FAK interactions with receptors such as IR/IGF1R/integrin and effectors such as PI3K/Akt/ERK are associated with lipid rafts. Formation and translocation of FAK-associated lipid complexes contributes to ACLY and FASN activation, channeling TCA-processed glucose to promote lipogenesis. Excessive lipid biosynthesis can induce cell growth and lipid turnover-mediated motility. Inhibition of ACLY and FASN leads to decreased lipid biosynthesis and tumor growth/invasion.

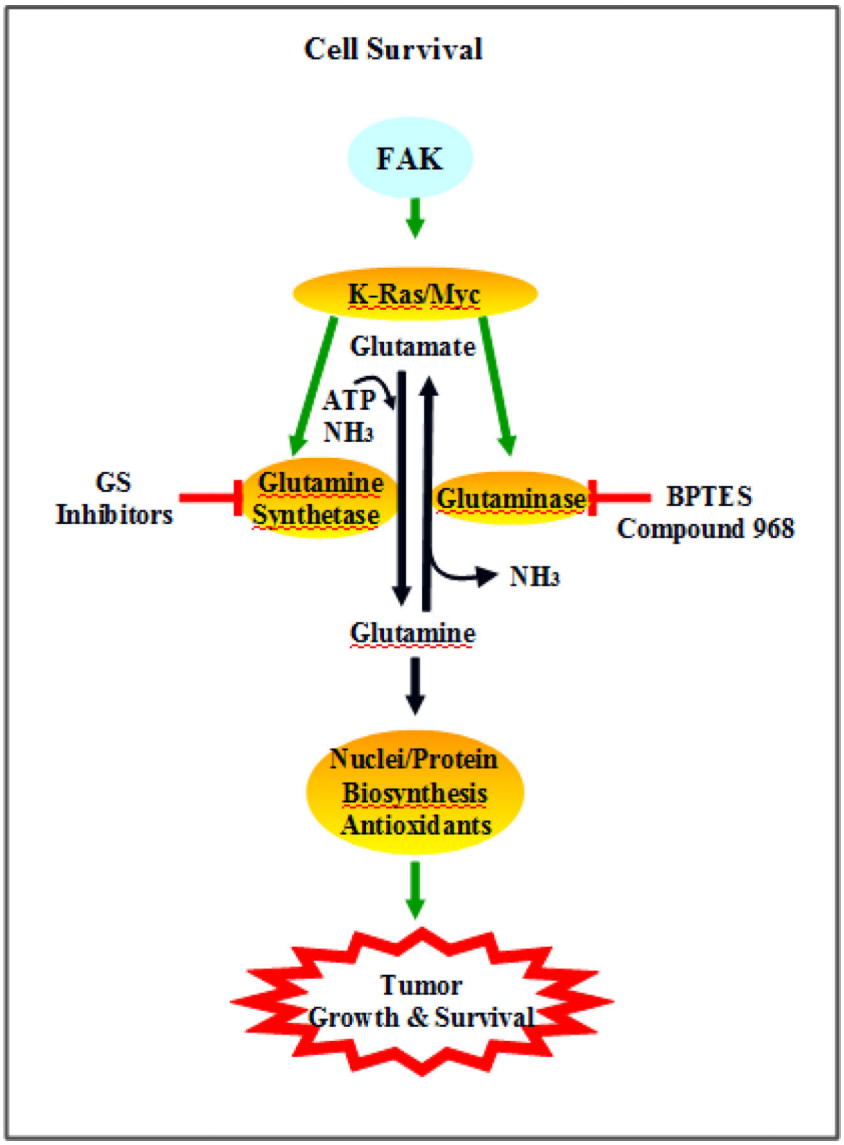

Fig 3. FAK activation and cancer dependency on glutamine.

FAK activation of oncogenes, K-Ras and Myc, alters the activities of glutamine synthetase and glutaminase. Increased glutamine flux provides precursors for nuclei acid and protein synthesis that are essential for cell proliferation. Furthermore, cancer cells rely on glutamine consumption to generate antioxidants, that neutralize rapid growth-accelerated ROS production, for their survival.

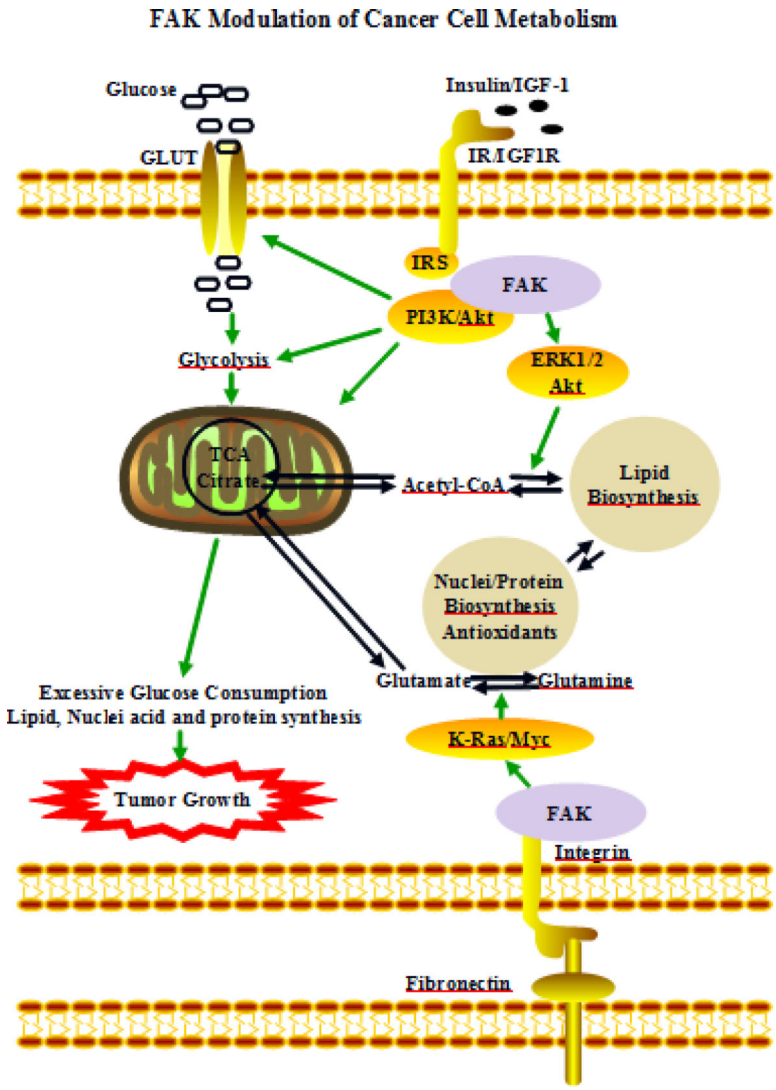

Fig 4. FAK modulation of cancer cell metabolism.

Insulin/IGF1 stimulates FAK-PI3K-Akt signaling through IRS. This modulates glucose metabolism via activation of glucose transporters, glycolytic and mitochondrial enzymes. Citrate can leave the TCA cycle in mitochondria and is converted to lipids. FAK activation of ERK/Akt can promote this conversion and channel glucose to lipids for the biosynthetic needs of rapidly growing cells. Anchorage-dependent stimulation of FAK activity contributes to K-Ras/Myc signaling-related glutamine metabolism.

Table 1.
Clinical trials of IGF1R inhibitors in subjects with cancer.

The NIH ClinicalTrials.gov database has been searched to identify studies on inhibitors targeting IGF1R signaling in solid tumors. Inhibitor names, tumor types, trial stages and their status/conclusions are summarized (clinicalTrial.gov)(Lacy, et al., 2008; Molife, et al., 2010; Scagliotti & Novello, 2012).

Name	Tumor	Trial phase/NIH number	Status/conclusion
PL225B	Advanced Refractory Solid Tumors	Phase 1/NCT01779336	Recruiting
OSI-906	Breast Cancer	Phase 2/NCT01013506	Withdrawn/toxicities and progressed
	Multiple Myeloma	Pahse 1 & 2/NCT01672736	Recruiting
	Lung Cancer	Phase 2/NCT01387386	Recruiting
AXL1717	Non Small Cell Lung Cancer	Phase 1/NCT01466647	Completed/No results posted
	Glioblastoma, Gliosarcoma	Phases 1 & 2/NCT01721577	Recruting
	Anaplastic Astrocytoma		
	Anaplastic		
	Oligodendroglioma		
	Anaplastic Oligoastrocytoma		
	Anaplastic Ependymoma		
	Non-small-cell Lung Cancer	Phase 2/NCT01561456	Recruiting
	Squamous Cell Carcinoma		
	Adenocarcinoma of the Lung		
	Solid Tumors Hematological Malignancies	Phase 1/NCT01062620	Completed/No results posted
CP-751,871	Carcinoma, Squamous Cell;	Phase 3/NCT00673049	Terminated/progressed
	Carcinoma,		
	Adenosquamous;		
	Carcinoma, Large Cell;		
	Carcinoma, Non-Small-Cell		
	Lung		
	Multiple Myeloma	Phase 1/NCT01536145	Completed/tolerated
	Solid Tumors	Phase 1/NCT00474760	Completed/tolerated
RAD001 AMG479	+ Neoplasm Metastases	Phase 1/NCT01122199	Recruiting
AVE1642	Liver Carcinoma	Phases 1 & 2/NCT00791544	Withdrawn/discontinued
MK-0646	Non Small Cell Lung Cancer	Phase 2/NCT00799240	On-going
	Pancreatic Cancer	Phases 1 & 2/NCT00769483	Recruiting
R1507	Neoplasms	Phase 1/NCT00400361	Completed/tolerated
XL228	Cancer, Lymphoma	Phase 1/NCT00526838	Terminated/discontinued