

**Imaging, Diagnosis, Prognosis**

**18FDG-PET Predicts Pharmacodynamic Response to OSI-906, a Dual IGF-1R/IR Inhibitor, in Preclinical Mouse Models of Lung Cancer**

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**Abstract**

**Purpose:** To evaluate 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography imaging (18FDG-PET) as a predictive, noninvasive, pharmacodynamic (PD) biomarker of response following administration of a small-molecule insulin-like growth factor-1 receptor and insulin receptor (IGF-1R/IR) inhibitor, OSI-906.

**Experimental Design:** *In vitro* uptake studies of 3H-2-deoxy glucose following OSI-906 exposure were conducted evaluating correlation of dose with inhibition of IGF-1R/IR as well as markers of downstream pathways and glucose metabolism. Similarly, *in vivo* PD effects were evaluated in human tumor cell line xenografts propagated in athymic nude mice by 18FDG-PET at 2, 4, and 24 hours following a single treatment of OSI-906 for the correlation of inhibition of receptor targets and downstream markers.

**Results:** Uptake of 3H-2-deoxy glucose and 18FDG was significantly diminished following OSI-906 exposure in sensitive tumor cells and subcutaneous xenografts (NCI-H292) but not in an insensitive model lacking IGF-1R expression (NCI-H441). Diminished PD 18FDG-PET, collected immediately following the initial treatment agreed with inhibition of pIGF-1R/pIR, reduced PI3K (phosphoinositide 3-kinase) and MAPK (mitogen activated protein kinase) pathway activity, and predicted tumor growth arrest as measured by high-resolution ultrasound imaging.

**Conclusion:** 18FDG-PET seems to serve as a rapid, noninvasive PD marker of IGF-1R/IR inhibition following a single dose of OSI-906 and should be explored clinically as a predictive clinical biomarker in patients undergoing IGF-1R/IR–directed cancer therapy. Clin Cancer Res; 17(10); 1–9. ©2011 AACR.

**Introduction**

The insulin-like growth factor-1 receptor (IGF-1R) is a tetrameric transmembrane receptor tyrosine kinase that is widely expressed in normal human tissues and is upregulated in a number of human cancers including colorectal, non–small cell lung, ovarian, and pediatric cancers. The receptor is composed of 2 α- and 2 β-subunits linked by disulfide bonds in which the extracellular α-subunit is responsible for ligand binding and the β-subunit consists of a transmembrane domain and a cytoplasmic tyrosine kinase domain. Ligand binding activates the tyrosine kinase activity of IGF-1R and results in trans-β-subunit autophosphorylation and stimulation of signaling cascades that include PI3K-mTOR and MAPK (mitogen activated protein kinase) pathways. Activation of IGF-1R has been reported to stimulate proliferation, survival, transformation, metastasis, and angiogenesis, whereas inhibition of IGF-1R has been shown to impede tumorigenesis in several human xenograft models (1).

Increased expression of IGF-1R and its cognate ligands, IGF-I and IGF-II, has been shown in a wide range of solid tumors and hematologic neoplasias relative to normal tissue levels. Epidemiologic studies have shown an increased risk for the development of colon, lung, breast, and bladder cancers with increased circulating levels of IGF-I (2–5). Additionally, IGF-1R expression levels have been correlated to poor prognosis in renal cell carcinoma (6, 7). IGF-1R signaling mechanism has also been linked to resistance to various antitumor therapies including epidermal growth factor receptor inhibitors (1, 6, 8, 9). Similarly, the insulin receptor (IR) is composed of a heterotetramer consisting of 2 extracellular α-subunits and 2 transmembrane β-subunits. Binding of insulin to the IR extracellular α-subunit causes a conformational change bringing together the 2 β-subunits. Activated IR tyrosine kinase phosphorylates several intracellular substrates including IRS-1-4, Shc, Gab1, and Cbl. These
Translational Relevance

The development of inhibitors targeting the insulin-like growth factor-1 receptor and insulin receptor (IGF-1R/IR) is a clinically important area of cancer research. OSI-906 is a potent and highly selective tyrosine kinase inhibitor now being evaluated in clinical studies that exhibits similar biochemical potency against IGF-1R (8 nmol/L) and IR (14 nmol/L), and is greater than 4 orders of magnitude more selective for IGF-1R/IR compared with a wide number of other receptor and nonreceptor kinases. Objective means to assess pharmacodynamic response to OSI-906 therapy in tumors remains challenging. To this end, we evaluated \(^{18}\)FDG-PET as a clinically relevant molecular imaging metric to quantify and predict pharmacodynamic response to OSI-906 in preclinical mouse models of lung cancer.

Phosphorylated proteins provide a docking site for effector proteins containing Src homology 2 (SH2) domains further linking IR to phosphoinositide 3-kinase (PI3K) via the regulatory p85 subunit. Homology between IR and IGF-IR ranges from 45% to 65% in the ligand binding domains to 60% to 85% in tyrosine kinase domains. Expression of IR is highest in adipose tissue and to a lesser extent in liver, heart, and muscle (10). Overexpression of IR in breast, colon, lung, ovarian, and thyroid cancers suggest a role of IR in tumor progression (10). More recently we have shown that forced overexpression of IR is tumorigenic in mice (11).

OSI-906 is a potent and highly selective tyrosine kinase inhibitor that exhibits similar biochemical potency against IGF-1R (8 nmol/L) and IR (14 nmol/L) and is greater than 4 orders of magnitude more selective for IGF-1R/IR compared with a wide number of other receptor and nonreceptor kinases (12). Within a panel of more than 180 kinases, only IGF-1R and IR were inhibited by greater than 50% at 1.0 \(\mu\)mol/L OSI-906. Inhibition of cell proliferation and induction of apoptosis following exposure to OSI-906 seems to be directly linked to inhibition of AKT in colorectal, lung, and pancreatic cancer cell lines (1, 12). In addition, OSI-906 has shown potent antitumor activity in vivo in several xenograft models (1). Because IGF-1R and IR pathway signaling is linked to glucose metabolism, we asked whether \(^{18}\)FDG-PET could function as a surrogate pharmacodynamic (PD) marker for OSI-906. To this end, we employed in vivo cell culture assays and in vivo animal models measuring uptake of radioactive glucose analogues as a function of treatment by OSI-906. Our data show that glucose uptake is rapidly inhibited in vivo and in vivo and tracks with IGF-1R, IR, and AKT inhibition after OSI-906 treatment in sensitive tumors. Moreover, reduced glucose uptake was readily observed after OSI-906 treatment in tumor tissues by using \(^{18}\)FDG-PET imaging methodologies. Hence, \(^{18}\)FDG-PET may function as a rapid, noninvasive tumor-specific PD marker for OSI-906 in the clinical setting where accurate assessment of PD effects is often limited by the lack of readily accessible tumor samples. Thus, \(^{18}\)FDG-PET may be a useful clinical tool in identifying active doses and patients potentially sensitive to this novel antitumor agent warranting further clinical investigation of this approach.

Materials and Methods

Cell lines

Human non–small cell lung carcinoma cell lines (NCI-H292, NCI-H441) were obtained from American Type Culture Collection. All cell lines were maintained in RPMI 1640 media (Mediatech) supplemented with 10% FBS (Sigma) and 1% sodium pyruvate (Mediatech) and maintained at 37°C and 5.0% CO₂. Cells were propagated to 80% to 90% confluency prior to in vitro and in vivo assays.

\(^{3}\)H-2-deoxy glucose uptake assay

Cells were seeded in 12-well tissue culture plates (Becton Dickinson) at a density of \(9.0 \times 10^5\) cells per well in normal glucose (11.1 mmol/L) media and allowed to attach for 6 to 8 hours at 37°C (n = 3 wells/group). The media was then changed to 5.5 mmol/L glucose media and the cells were allowed to equilibrate overnight. Three hours prior to the assay, the media was again removed and replaced with media containing 0.0 mmol/L glucose (glucose starvation). The cells were then treated with varying concentrations of OSI-906 (0.0–30 \(\mu\)mol/L) and 0.15 mCi of \(^{3}\)H-2-deoxy glucose (Perkin Elmer). After 30 minutes, the media was removed, the cells placed on ice, and washed once with ice-cold PBS (Mediatech). The PBS was then removed and the cells were lysed in radioimmunoprecipitation assay buffer (Sigma) for 15 minutes on ice. The lysates were harvested and counted in a Beckman LS6500 Liquid Scintillation counter (Fullerton). \(^{3}\)H-2-deoxy glucose uptake was calculated as raw counts and normalized to control samples (0.0 \(\mu\)mol/L OSI-906). As a positive control of glucose uptake inhibition, NCI-H292 cells were treated with increasing concentrations (2.5–10 \(\mu\)mol/L) of cytochalasin B (Sigma), a known inhibitor of GLUT1 and GLUT4 glucose transporters.

Mouse models

Studies involving mice were conducted in accordance with federal and institutional guidelines. NCI-H292 and NCI-H441 non–small cell human xenograft tumors were generated as described (13). Briefly, \(4 \times 10^6\) cells were injected subcutaneously on the right flank of 5- to 6-week-old female athymic nude mice (Charles Rivers). Using this method, palpable tumors were typically observed within 2 weeks following injection of cells and were allowed to progress until approximately 150 to 200 mm³, and then randomized for treatment studies. Measurement of volume was done by using high-resolution ultrasound imaging as described (14). Mice were treated when the tumors reached approximately 200 mm³ in volume. Blood glucose was measured by a Freestyle digital glucose meter and test strips.
(Abbott) before and at 2 hours, and 4 hours after treatment with 60 mg/kg OSI-906 or 25 mmol/L tartaric acid vehicle.

**Procurement of **\(^{18}\)FDG

\(^{18}\)FDG was synthesized in the Vanderbilt University Medical Center Radiopharmacy and distributed by PET-NET. The average radiochemical purity of the product was 98.5% and specific activity was more than 1,000 Ci/mmol.

**\(^{18}\)FDG-PET imaging**

Animal handling methods in preparation for and during \(^{18}\)FDG-PET imaging were similar to the published protocols (15–17). Briefly, before imaging, mice were fasted overnight and allowed to acclimate to the PET imaging facility environment for at least 1 hour in a warmed chamber at 31.5°C. Mice were administered a single dose of OSI-906 at 60 mg/kg in a 25 mmol/L tartaric acid vehicle via oral gavage \((n = 8/group)\). \(^{18}\)FDG was administered via a single retro-orbital injection of approximately 200 \(\mu\)Ci \((100 \mu\)L) and imaged 2, 4, and 24 hours postdosing of OSI-906, or 4 hours after tartaric acid vehicle. Mice were conscious during the uptake period and maintained in a warmed chamber. Following a 50-minute uptake period, 10-minute static PET scans were collected on a Concorde Microsystems micro-PET Focus 220 (Siemens). Mice were sacrificed and tissues collected for molecular analysis. Immunoprecipitation/Western blot analysis. Tumor or cell lysate samples were separated on SDS-PAGE and immunoblotted with a total IGF-1R antibody (Cell Signaling) followed by detection by enhanced chemiluminescence (GE Healthcare Life Sciences). The blots were reprobed with total IR antibody (Cell Signaling). Phosphorylated IGF1-R and IR bands were quantified by an Image Quant LAS 4000 with Image Quant TL 7.0 software (GE Healthcare Life Sciences).

Markers of altered glycolysis were analyzed by Western blot analysis. Tumor or cell lysate samples were separated on SDS-PAGE, immunoblotted, and detected by using enhanced chemiluminescence (GE Healthcare Life Sciences). The antibodies included pAKT (Ser473), total AKT, pS6 (Ser235/236), pERK 1/2, total ERK 1/2, (Cell Signaling), and \(\beta\)-actin (Sigma). The phosphorylated to total signal intensities were quantified as described earlier.

**Receptor tyrosine kinase analysis**

Tumor lysates were prepared according to the manufacturer’s protocol (Proteome Profiler; R&D Systems) in NP-40 lysis buffer and clarified by centrifugation. The samples were incubated with the Human Phospho-RTK Array at 2,000 \(\mu\)g total protein overnight at 4°C with rocking. The arrays were developed by SuperSignal FEMTO ECL detection (Pierce). The phospho-spots on the receptor tyrosine kinase (RTK) blot were quantified by using Image Quant LAS 4000 with Image Quant TL 7.0 software (GE Healthcare Life Sciences).

**Results**

**Sensitivity of NCI-H292 and NCI-H441 to OSI-906**

Non–small cell lung cancer is a potentially attractive indication for OSI-906 due to the implication of IGF1R/IR as a driver in this, as well as drug resistance in this setting. We established sensitivity of the NCI-H292 and NCI-H441 xenograft models to OSI-906 in vivo by measuring tumor volumes longitudinally with high-resolution ultrasound imaging. Daily treatment with 60 mg/kg OSI-906 over 10 days resulted in tumor growth inhibition in the NCI-H292 xenografts compared with controls (Fig. 1A), but no growth changes were observed in the nonresponsive NCI-H441 xenografts (Fig. 1B). We found that NCI-H292 tumors had considerably higher levels of pIGF1-IR and pIR than NCI-H441 tumors (Fig. 1C).

**Inhibition of \(^{3}\)H-2-deoxy glucose uptake in vitro**

We assessed the effect of OSI-906 treatment on uptake of \(^{3}\)H-2-deoxy glucose in NCI-H292 and NCI-H441 cells in vitro. Cells were treated for only 30 minutes with OSI-906 to avoid potential antiproliferative effects of the drug to
interfere with this endpoint analysis. OSI-906 treatment resulted in a rapid and dose-dependent inhibition of uptake of the radiotracer in the NCI-H292 cell line (Fig. 2A). The percent inhibition ranged from 12% to 60% as the dose increased from 1.0 to 30 \( \mu \text{mol/L} \) OSI-906. In comparison, the NCI-H441 cell line showed a reduced sensitivity to OSI-906. For the NCI-H292 cell line a 35% decrease in uptake of \( ^3\text{H}-2\)-deoxy glucose was achieved at 10 \( \mu \text{mol/L} \) OSI-906, whereas in the NCI-H441 cell line the same decrease of the radiotracer was observed at only 30 \( \mu \text{mol/L} \) OSI-906 (Fig. 2B). Analysis for cell death by fluorescence-activated cell sorting by using the Invitrogen Live/Dead assay determined no significant cell death at all OSI-906 concentrations (1.0–30 \( \mu \text{mol/L} \)) tested compared with 0.05% dimethylsulfoxide controls (data not shown). As a positive control, cytochalasin B (2.5–10 \( \mu \text{mol/L} \)) was administered to the NCI-H292 cells and evaluated for \( ^3\text{H}-2\)-deoxy glucose uptake in an analogous manner. Figure 3C shows that cytochalasin B significantly inhibits uptake of the radiotracer by 85% to 90% in this cell line, and that the inhibition of \( ^3\text{H}-2\)-deoxy glucose by OSI-906 in NCI-H292 cells represents a rapid PD effect.

**Correlation with target-pathway inhibition in vitro**

NCI-H292 cell lysates were treated with an increasing concentration of OSI-906 (0.0–10 \( \mu \text{mol/L} \)) for 30 minutes and then analyzed for pIGF-1R, pIR, pERK 1/2, pAKT, pS6, and \( \beta \)-actin as shown in Figure 2D. We observed a significant decrease in phosphorylation of AKT and S6, suggesting a correlation between decreased glucose uptake and inhibition of targets downstream of IGF-1R and IR. NCI-H292 cells treated at lower concentrations (10 nmol/L to 5 \( \mu \text{mol/L} \)) over 2, 12, and 24 hours showed target inhibition at all concentrations at 2 hours, and sustained inhibition of pIGF-1R at both 12 and 24 hours for all concentrations except 10 nmol/L (Fig. 3).

**Inhibition of \( ^{18}\text{FDG} \) uptake in vivo**

\( ^{18}\text{FDG} \)-PET images of mice bearing the NCI-H292 and NCI-H441 xenografts are shown in Figure 4A. The NCI-H292 xenografts (sensitive to OSI-906 treatment) show a significant decrease (\( P < 0.05 \)) in \( ^{18}\text{FDG} \) uptake at 2, 4, and 24 hours postdosing with OSI-906 compared with vehicle-treated controls. NCI-H441 xenografts (insensitive to OSI-906 treatment) did not show a significant change in uptake of \( ^{18}\text{FDG} \) at any time point evaluated. Graphically, these results are shown in Figure 4B and C. The decreased %ID/g in the NCI-H292 xenografts is suggestive of a rapid PD effect observed by \( ^{18}\text{FDG} \) imaging mediated by the inhibition of IGF-1R and IR pathways by OSI-906. Conversely, for the NCI-H441 xenograft model no difference in uptake of the radiotracer was observed in the tumor samples between vehicle controls and the OSI-906 treatment group.

**Correlation with target-pathway inhibition**

Target inhibition of both pIGF-1R and pIR by a single dose of OSI-906 at 60 mg/kg \textit{in vivo} in NCI-H292 xenograft tumors is shown in Figure 5A. The data show that at 2 and 4 hours posttreatment target inhibition of pIGF-1R is greater than 80%, with 30% inhibition observed at 24 hours (Fig. 5B). The effect on pIR is equally pronounced, showing significant target inhibition of this receptor. Target inhibition of pIR was greater than 80% at 4 hours posttreatment with 40% inhibition observed at 24 hours. Inhibition of both target receptors correlated with decreased uptake of \( ^{18}\text{FDG} \) in the same tumor samples analyzed. Figure 5C shows the results of a Western blot from tumor lysates at selected time points from mice bearing the NCI-H292 xenografts that were treated with 60mg/kg OSI-906 (\( n = 4/\text{group} \)). We found reduced activation levels of targets involved in glycolysis that are downstream of IGF-1R and IR, including pAKT, pS6, and pERK 1/2 as measured 4 hours posttreatment with OSI-906.
compared with untreated control lysates. Importantly, Western blot analysis of OSI-906–treated NCI-H441 tumor xenografts, which do express very low levels of the target receptor, showed no reduction in pAKT levels at any time point compared with control (Supplementary Fig. S1).

Pharmacokinetic analysis
Table S1 shows the drug concentration in the plasma samples from the NCI-H292 xenografts remained at a constant concentration approximately 20 μmol/L for 2 to 8 hours postdosing. By 24 hours postdosing, the level of OSI-906 in the plasma had decreased by approximately 60% to approximately 6.5 μmol/L, resulting in some potential loss of target coverage with time.

Discussion
Catabolism of glucose through the tricarboxylic acid cycle in normal cells is the preferred method of ATP production leading to cell proliferation and survival. It is
now well known that many cancer cells avidly consume glucose and produce lactic acid for ATP production despite the inefficiency of this metabolic pathway. The reason why cancer cells utilize a less efficient means of ATP production remains elusive; however, recent studies suggest that in cancer cells an increase in glycolysis, in addition to respiration, can generate energy more quickly than normal cells that rely on respiration alone. As a result, this high rate of glucose metabolism by cancer cells has resulted in the wide use of $^{18}$FDG PET to image and diagnose rapidly dividing cells including tumors (18).

Both IGF-1R and IR signal through the PI3K signaling pathway. PI3K is linked to both growth control and glucose metabolism. PI3K directly regulates glucose uptake and metabolism via AKT mediated regulation of glucose transporter activation and expression (GLUT1 and GLUT4), enhanced glucose capture by increased hexokinase activity, and stimulation of phosphofructokinase activity (19–22). PI3K activation thus renders cells dependent on glucose leading to glucose addiction. In normal cells, activation of PI3K/AKT is highly controlled by dephosphorylation of phosphatidylinositol by PTEN. However, in many cancers, PTEN is lost leading to constitutive activation of the PI3K pathway (23). Moreover, activation of this pathway can be enhanced by other mechanisms, which, when combined, can constitute some of the more prevalent classes of mutations in human malignancy (e.g., PI3CA, AKT2, BCR-ABL, HER2/neu). Therefore, activation of AKT is likely the most important signaling event in relation to cellular metabolism, because AKT is sufficient to drive glycolysis and lactate production, as indicated by the following diagram.
formation and suppress macromolecular degradation in cancer (23, 24). It has been shown that various therapeutic agents that disrupt the PI3K/AKT pathway, either directly or upstream of PI3K/AKT, lead to decreased glucose uptake in tumors as measured by $^{18}$FDG-PET (25). Furthermore, the ability to inhibit FDG uptake in tumors has been shown to correlate well with treatment response in a number of cancers. As a consequence, $^{18}$FDG-PET has been used clinically in cancer patients to predict response to various therapies via the ability of agents to disrupt glucose metabolism and glucose uptake in tumors (22, 26–28).

The primary purpose of these studies was to determine whether $^{18}$FDG-PET could be used as an early, noninvasive PD biomarker for the dual kinase inhibitor OSI-906. We first determined in vitro using the sensitive cell line, NCI-H292 that a rapid decrease in $^3$H-2-deoxy glucose uptake was observed in a dose-dependent manner after treatment with pharmacologically relevant concentrations of OSI-906. In the NCI-H441 cell line reduced sensitivity to equimolar concentrations of OSI-906 was observed for the same assay. NCI-H292 cell lysates were then probed for markers of altered glycolysis by Western blot analysis and showed a significant reduction in pIGF-1R, pIR, pAKT, pS6, and pERK 1/2. Target inhibition of these markers strongly link IGF-1R and IR to the PI3 kinase and AKT pathways and resultant changes in metabolic activity of cultured cells when exposed to OSI-906.

In vivo, decreased uptake of $^{18}$FDG was observed rapidly at 2, 4, and 24 hours after administration of an efficacious dose of 60 mg/kg of OSI-906 in NCI-H292 tumor–bearing animals. In comparison, the insensitive NCI-H441 xeno-grafts showed no change in uptake of the radiotracer at the same time points and same dosage. Analysis of target inhibition of pAKT, pS6, pERK 1/2, pIGF-1R, and pIR from NCI-H292 tumor lysates was carried out by Western blot and RTK array analysis. The results showed strong target inhibition of these markers at 4 hours postadministration of a single 60 mg/kg dose of OSI-906, further corroborating the link of metabolic activity of tumors with IGF-1R and IR signaling pathways. Specific target inhibition of pIGF-1R and IR by RTK array analysis resulted in significant ($P < 0.05$) reduction of these phospho-targets (>80%) at 2 and 4 hours postadministration of the agent, and correlated to reduced uptake of $^{18}$FDG. Blood glucose levels of non–tumor-bearing mice appeared elevated from a baseline, fasted level following 2 and 4 hours of 60mg/kg OSI-906 treatment; however, the increased levels were not statistically significant ($P > 0.5$). As expected, similarly evaluated vehicle-treated mice did not exhibit elevated glucose levels when evaluated at 2 and 4 hours (Supplementary Fig. S2A). Importantly, $^{18}$FDG uptake in NCI-H441 tumors, which are insensitive to OSI-906, was similar in both OSI-906–treated and vehicle-treated tumors. The fact that posttreatment $^{18}$FDG uptake in these mice was not decreased when compared with baseline imaging suggests that the somewhat elevated circulating glucose levels had no detectable impact on $^{18}$FDG uptake in this study. As further evidence, no change in $^{18}$FDG uptake was seen in skeletal muscle following OSI-906 (Supplementary Fig. S2B), and only a slight increase in liver $^{18}$FDG uptake was seen at 2 and 4 hours before returning to baseline at 24 hours (Supplementary Fig. S2C).
Fig. S2C). Nonetheless, it is possible that human trials incorporating 18FDG PET as a biomarker of response to OSI-906 may benefit from measurement of blood glucose levels, as the effects on 18FDG uptake in patient studies could be larger than we observed in mice.

The present findings support a strong link of rapidly altered metabolic activity in both cultured cells and in vivo tumors induced by target inhibition of the IGF-1R and IR signaling pathways. Though there is still much to be learned how cellular metabolism in proliferating cells is regulated, there is an ever increasing body of information supporting increased communication between signaling pathways and metabolic control of the cell. These studies suggest that 18FDG-PET has potential to serve as a rapid, noninvasive biomarker of PD effects of OSI-906 in patients treated with this dual IGF-1R/IR kinase inhibitor. This method may be most beneficial in early clinical development where accurate assessment of PD effects is often limited by the lack of readily accessible tumor samples. Thus, 18FDG-PET may be a useful clinical tool in identifying active doses and patients potentially sensitive to this novel antitumor agent and perhaps other compounds of this target class. Currently, 18FDG-PET imaging is being employed in several clinical trials as a biomarker for early efficacy of OSI-906.

Disclosure of Potential Conflicts of Interest

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References

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