The Insulin-Like Growth Factor-I Receptor Kinase Inhibitor, NVP-ADW742, Sensitizes Small Cell Lung Cancer Cell Lines to the Effects of Chemotherapy

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ABSTRACT

Purpose: Insulin-like growth factor-I (IGF-I) is a potent growth factor for small cell lung cancer (SCLC) in both the autocrine and endocrine context. It also inhibits chemotherapy-induced apoptosis through activation of the phosphatidylinositol 3-kinase (PI3K)-Akt pathway and we have previously shown that inhibition of this signaling pathway enhances sensitivity of SCLC cell lines to chemotherapy. The purpose of this study was to determine whether the novel IGF-I receptor (IGF-IR) kinase inhibitor, NVP-ADW742, sensitizes SCLC cell lines to etoposide and carboplatin, which are commonly used in the treatment of SCLC.

Experimental Design: Cell growth in the presence of various combinations of NVP-ADW742, imatinib (STI571; Gleevec/Glivec), and chemotherapeutic agents was monitored using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and analyzed using the Chou-Talalay multiple-drug-effect equation. Induction of apoptosis was assessed using terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) and Western blot analysis of procaspase 3 and poly(ADP-ribose)polymerase cleavage. IGF-I-induced vascular endothelial cell growth factor expression was monitored by Northern blot and ELISA.

Results: NVP-ADW742 synergistically enhanced sensitivity of multiple SCLC cell lines to etoposide and carboplatin. Maximal enhancement occurred at concentrations of NVP-ADW742 that eliminated basal PI3K-Akt activity in individual cell lines. In the WBA cell line, in which the c-Kit receptor tyrosine kinase is partly responsible for basal PI3K-Akt activity, the combination of NVP-ADW742 and imatinib was superior to NVP-ADW742 alone in sensitizing the cells to etoposide. Enhancement of the sensitivity of SCLC cell lines to etoposide, as determined by MTT assay, correlated closely with sensitization to the induction of apoptosis as measured by TUNEL and caspase activation assays. Treatment with NVP-ADW742 also eliminated IGF-I-mediated expression of vascular endothelial cell growth factor, suggesting that in addition to enhancing sensitivity of SCLC to chemotherapy, this kinase inhibitor could potentially inhibit angiogenesis in vivo.

Conclusions: Inhibition of IGF-IR signaling synergistically enhances the sensitivity of SCLC to etoposide and carboplatin. This enhancement in sensitivity to chemotherapy tightly correlates with inhibition of PI3K-Akt activation. Future SCLC clinical trials incorporating IGF-IR inhibitors alone or in combination with other kinase inhibitors should include assessment of PI3K-Akt activity as a pharmacodynamic end-point.

INTRODUCTION

Small cell lung cancer (SCLC) accounts for ~15% to 20% of all lung cancers and currently causes the demise of >90% of affected individuals within 5 years (1, 2). Paradoxically, SCLC is a highly chemotherapy-responsive disease, with a variety of multidrug combinations producing response rates of >80%, with a third or more being complete responses (3). Trials of chemotherapy dose escalation have resulted in minimal increases in response rates and increased toxicity without a survival advantage (4, 5). Likewise, improvements in response by addition of paclitaxel to the standard combination of cisplatin and etoposide came at the expense of increased toxicity without significant improvement in long-term survival (6, 7). Substitution of novel cytotoxic drugs such as irinotecan may result in prolongation of median survival (8) but improvement in long-term survival will likely depend on the development of new therapeutic approaches which can prevent or overcome the development of clinical resistance to cytotoxic agents. One promising approach is to utilize agents that target molecular abnormalities that regulate growth and resistance to apoptosis in SCLC.

A common molecular abnormality in SCLC is the presence of multiple autocrine loops, with one of the most prominent involving coexpression of insulin-like growth factor-I (IGF-I) and its receptor. Stimulation of the IGF-IR by IGF-I or IGF-II is an important factor in the establishment and maintenance of the malignant phenotype and results in potent stimulation of the antiapoptotic phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway (9, 10). Epidemiologic studies have shown that increased serum levels of IGF-I and decreased levels of its predominant binding protein, IGFBP-3, correlate with an increased risk for several types of cancers (11, 12). In particular, high plasma levels
of IGF-I are associated with a 2.75-fold increased risk of lung cancer, whereas high plasma levels of IGFBP-3 are associated with a reduced risk compared with control subjects (13). IGF-I has also been shown to be an important regulator of VEGF expression and angiogenesis in several cancers, including SCLC (14, 15). IGF-I is an important growth factor for SCLC cells both in the endocrine and autocrine context (16–18). We have also shown that it blocks apoptosis induced by imatinib, a potent inhibitor of the c-Kit receptor tyrosine kinase (19), which with its ligand, stem cell factor, constitutes another relevant autocrine loop in SCLC (19–21). Based on these observations, we investigated targeting the IGF-IR using a low molecular mass selective kinase inhibitor (22).

NVP-ADW742 is an ATP-competitive inhibitor that inhibits IGF-IR autophosphorylation with a cellular IC_{50} of 0.1 to 0.2 μmol/L, which is ~16-fold lower than that of the insulin receptor (23, 24). Although this compound also inhibits c-Kit kinase activity with an IC_{50} in the 3 to 5 μmol/L range, its cellular IC_{50} against the epidermal growth factor receptor, platelet-derived growth factor receptor, and VEGF receptor-2 exceed 10 μmol/L. Biochemical screening against a broad panel of tyrosine and serine/threonine kinases showed at least a 10-fold selectivity for the IGF-IR. Exceptions were Flt-1, Flt-3, and Tek (23) but there is no evidence that these three kinases are expressed in SCLC (24). Using a representative panel of SCLC cell lines, we previously characterized two populations by their differential sensitivity to NVP-ADW742 (24).

Exceptionally, IGF-IR and c-Kit kinase activities. In the latter population, but not the former, the combination of imatinib and NVP-ADW742 was highly synergistic with regards to inhibition of growth and induction of apoptosis. Importantly, this synergism seemed to reflect synergistic inhibition of PI3K-Akt signaling. In the sensitive population, NVP-ADW742 alone was sufficient to eliminate Akt activation, but in the more resistant population, elimination of Akt activity required both NVP-ADW742 and imatinib. These data indicated that some SCLC cell lines were solely dependent on IGF-IR signaling for Akt activation but in others, either IGF-IR or c-Kit could activate Akt to generate proliferative and survival signals.

We have also previously shown that Akt signaling, which is dependent on PI3K activation, is critical for both promoting proliferation and inhibiting apoptosis in SCLC (25). Constitutive activation of Akt stimulated proliferation to a level approximating that induced by serum and inhibition of PI3K or Akt by either biochemical or molecular means resulted in a dose-dependent inhibition of growth. Perhaps more importantly for therapeutic purposes, partial inhibition of this pathway using the PI3K inhibitor LY294002 was markedly synergistic with etoposide in increasing apoptosis and decreasing clonogenic growth. Because IGF-IR seems to be an important activator of the PI3K-Akt pathway in all SCLC cell lines and the predominant activator in some, the goal of the present study was to determine whether NVP-ADW742 would enhance the efficacy of standard chemotherapeutic agents used for the treatment of SCLC. When combined with either etoposide or carboplatin, NVP-ADW742 synergistically inhibited the growth of and induced apoptosis in multiple SCLC cell lines. The enhancement of the efficacy of the chemotherapeutic agents correlated with inhibition of Akt activation by the kinase inhibitor. In the WBA cell line where NVP-ADW742 only partially inhibited Akt activity, addition of imatinib to NVP-ADW742 further enhanced cytotoxicity. In addition to sensitizing SCLC cell lines to chemotherapy, NVP-ADW742 also blocked IGF-I-mediated VEGF expression. These data suggest that IGF-IR inhibitors could markedly enhance the efficacy of standard chemotherapy in SCLC.

**MATERIALS AND METHODS**

**Compounds.** Imatinib and NVP-ADW742 were synthesized and provided by Novartis Pharma AG (Basel, Switzerland).

Stock solutions of these compounds and etoposide (Calbiochem-Novabiochem, La Jolla, CA) were made in DMSO (Sigma Chemical Co., St. Louis, MO) and diluted with culture media before use. Carboplatin (Sigma) was dissolved in H2O. The final DMSO concentration in all cultures, including vehicle controls, was 0.1%.

**Cell Growth Assays.** The H526, H146, WBA, and H209 SCLC cell lines (26, 27) were cultured in complete medium consisting of 10% (v/v) fetal bovine serum (FBS) (Life Technologies, Invitrogen Corporation, Carlsbad, CA), 2 mmol L-glutamine (Bio-Whittaker, Walkersville, MD) and 50 units/mL penicillin-streptomycin (Bio-Whittaker) in RPMI 1640 medium (Life Technologies, Invitrogen). Where indicated, when cells were grown under serum deprivation conditions, 0.1% bovine serum albumin (Sigma) was added to the medium. Cell growth was measured using the 3-(4,5 dimethylthiazol-2-yl)-2, 5-diphenyl-tetrazolium bromide (MTT; Sigma) colorimetric dye reduction method (28). Duplicate plates containing eight replicate wells per assay condition were seeded at a density of 1 × 10^4 cells in 0.1 mL of medium and data was expressed as the percentage of change in absorbance at 540 nm over 72 hours, relative to initial values obtained 3 hours after plating. For each experiment, a dose-response curve was generated by plotting the percentage of change in growth relative to control treatment against inhibitor concentration. For assessment of efficiency of growth inhibition, an IC_{50} value was calculated using the dose-response curve. These data were also used in calculation of the combination index (CI) to measure the degree of synergism according to the Chou-Talalay multiple-drug-effect equation (29) using CalcuSyn software (Biosoft, Ferguson, MO). Growth effects at different drug concentrations were analyzed for statistical significance using a Student’s two-tailed t test.

**Western Blotting Assays.** To monitor caspase 3 and poly(ADP-ribose)polymerase (PARP) cleavage, SCLC cells in complete medium were treated with either NVP-ADW742 or a chemotherapeutic agent (etoposide and carboplatin) or a combination for 24 hours. To determine the effect of combination drug treatments on Akt activation, the cells were quiesced overnight in serum-free medium and pretreated with NVP-ADW742 for 1 hour followed by treatment in 10% FBS for 6 hours in the absence or presence of the indicated chemotherapeutic agent. At the end of the treatment period, whole cell lysates were prepared by resuspending the cells in cold SDS sample buffer [1% SDS, 0.04 mol/L Tris-HCl (pH 6.8), 5% glycerol].
The lysates were boiled and sheared through a 25-gauge needle and protein concentrations were determined using a commercial assay kit (bicinchoninic acid; Pierce Biotechnology, Inc., Rockford, IL). Fifty micrograms of protein were resolved on 10% polyacrylamide gel and transferred to polyvinylidene difluoride membranes. The membranes were probed with either anti-cleaved PARP, PARP, cleaved caspase 3, caspase 3, or pAkt (Ser473; Cell Signaling, Beverly, MA), β-actin (Sigma) and pan-Akt (Santa Cruz Biotechnology, Santa Cruz, CA) antibodies. Signals were detected using the West Pico chemiluminescent system (Pierce Biotechnology) with the aid of a Raytest (New Castle, DE) cooled CCD camera imaging system and the Aida 2.0 software package.

**Terminal Deoxynucleotide Transferase-Mediated dUTP Nick End Labeling Assay.** H526 cells were treated with the indicated drug combination for 24 hours in complete medium followed by addition of 5 μmol/L cell tracker orange (Molecular Probes, Eugene, OR) for 30 minutes to readily allow identification of individual cells with fluorescence optics. Cells were washed in PBS and reincubated for a further 30 minutes in complete medium and cytosin cell preparations were made. The cells were fixed, permeabilized and free DNA 3’ ends were labeled with fluorescein-conjugated dUTP mediated by terminal deoxynucleotide transferase using the *in situ* cell death detection kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer’s instructions. Independent 400 × fields containing a total of at least 500 cells were evaluated for nuclear labeling by fluorescence microscopy for each treatment. Cells treated with 25 μmol/L etoposide were used as a positive control.

**Vascular Endothelial Growth Factor Expression.** H526 cells were quiesced in serum-free medium overnight, pretreated with NVP-ADW742 or DMSO vehicle for 1 hour prior to incubation with 10 ng/mL IGF-I or 10% FBS for 24 hours in the presence of DMSO or NVP-ADW742. The culture medium was assayed for VEGF using a commercial ELISA (R&D Systems, Minneapolis, MN). Northern analysis was done using 10 μg of total cellular RNA isolated from cells treated as above to assess VEGF mRNA levels, as previously described (15). VEGF mRNA was quantitated using a Raytest phosphoimaging station and the Aida 2.0 software package. The VEGF signal intensity in each lane was normalized to that of β-actin and presented as a relative proportion to the vehicle control, which was assigned a value of 1.

**RESULTS**

**NVP-ADW742 Combined with Etoposide and Carboplatin Synergistically Inhibits Small Cell Lung Cancer Growth and Induces Cytotoxicity.** The effect of combining NVP-ADW742 with etoposide was assessed by 72-hour MTT assay using the H526, H146, WBA, and H209 cell lines. Concentrations of NVP-ADW742 bracketing the cell line-specific IC_{50} for the drug were combined with clinically relevant concentrations of the chemotherapeutic agent. In the H526 and H146 cell lines, basal Akt activity in serum-containing medium is driven primarily by the IGF-IR, whereas in WBA and H209 both the IGF-IR and c-Kit seem to drive Akt activity (24). Therefore, the concentrations of NVP-ADW742 required to inhibit Akt activity and growth were 10-fold higher (approxi-
additive combination of the actions of each agent individually, especially with regard to PARP cleavage. The combination of NVP-ADW742 with 5 μmol/L etoposide also produced equivalent PARP cleavage to 25 μmol/L etoposide in the WBA cell line (Fig. 3C). Thus, the combination of NVP-ADW742 with a low concentration of etoposide resulted in an additive if not synergistic induction of apoptosis.

The Combination of NVP-ADW742 and Imatinib Enhances The Cytotoxic Response to Etoposide. WBA is a cell line that is resistant to both etoposide and carboplatin, which fails to induce a net cytotoxic response even at high concentrations (Figs. 1C and 2C). This cell line is also relatively resistant to NVP-ADW742, with an IC₅₀ in excess of 5 μmol/L. The reason for this resistance to IGF-IR inhibition seems to be attributable to the fact that the IGF-IR is only partially responsible for PI3K-Akt activity in this cell line, with significant residual Akt activity (Fig. 1C) present at concentrations of NVP-ADW742 in 10-fold excess of the IC₅₀ for the IGF-IR. We have previously shown that addition of imatinib to NVP-ADW742 resulted in a marked reduction in PI3K-Akt activity and enhancement of growth inhibition and cytotoxicity in WBA, which suggests that the combined actions of the IGF-IR and c-Kit support basal Akt activity, growth, and survival in this cell line (24). In fact, induction of apoptosis by the combination of imatinib (5 μmol/L) with NVP-ADW742 (5 μmol/L) approached that induced by 25 μmol/L etoposide (24). We hypothesized that combination of these two kinase inhibitors should enhance sensitivity to etoposide to a greater extent than NVP-ADW742 alone based on the greater inhibition of PI3K-Akt activity achieved by the kinase inhibitor cocktail. To test this hypothesis, we generated a dose-response curve for etoposide in the presence of 5 μmol/L of each individual kinase inhibitor alone, as well as in combination. As previously observed (24) and illustrated in Fig. 4, the combination of imatinib with NVP-ADW742 was highly synergistic and cytotoxic, with a nearly 40% reduction in cell number over the
course of the MTT assay. This is in comparison to the effects of 10 μmol/L etoposide alone, which produced a net cytostatic response, indicating that the combination of kinase inhibitors alone is highly efficacious in this cell line. As previously reported (19), addition of imatinib to etoposide did not sensitize the cells to etoposide. However, the combination of imatinib, NVP-ADW742, and 10 μmol/L etoposide resulted in a doubling of the cytotoxic response seen with the kinase inhibitor combination alone and a marked enhancement of the response compared with etoposide alone ($P < 0.0001$). The efficacy of the kinase inhibitor cocktail in enhancing sensitivity to etoposide correlated very well with a further reduction in Akt activity relative to the reductions induced by the individual kinase inhibitors (Fig. 4B and C).

**NVP-ADW742 Blocks Insulin-like Growth Factor-I-Mediated Vascular Endothelial Growth Factor Expression.**

IGF-I is one of the more potent growth factors that regulates VEGF expression and subsequent angiogenesis, which plays a critical role in tumor progression, metastasis, and chemosensitivity (30). The effect of IGF-I is independent and additive with that of hypoxia and is a result of induction of VEGF transcription mediated by enhanced expression of the HIF-1α transcription factor (14, 31). To determine whether such a mechanism was operative in SCLC, quiescent H526 cells were treated with IGF-I in the presence or absence of NVP-ADW742 (5 μmol/L) for 24 hours. Total RNA was extracted from the cells for Northern blot analysis and the conditioned medium was analyzed for VEGF protein by ELISA. Figure 5A illustrates a representative Northern blot demonstrating that IGF-I induced a doubling of VEGF mRNA expression, which was completely inhibited by NVP-ADW742. The drug had no effect on basal expression of VEGF mRNA by this cell line grown in serum-free medium. The ELISA for secreted VEGF (Fig. 5B) correlates very well with the mRNA expression data and confirms that NVP-ADW742 completely inhibits the potent induction of VEGF by IGF-I. The drug also inhibited VEGF expression mediated by 10% FBS, which contains IGF-I in addition to many other growth factors (Fig. 5C). Addition of supplemental IGF-I to FBS produced no significant increase in VEGF expression compared with FBS alone. NVP-ADW-742 treatment also returned VEGF expression to basal levels in the presence of IGF-I-supplemented FBS. Taken together, these observations strongly suggest that the predominant component in FBS that enhances VEGF expression is IGF-I. Furthermore, these observations suggest that even in a milieu containing a complex mix of growth factors in addition to IGF-I, as would likely be encountered in vivo, NVP-ADW742 can inhibit VEGF expression and therefore could have an important antiangiogenic effect.

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**Fig. 2** Sensitivity to carboplatin is synergistically enhanced by NVP-ADW742. MTT assays were performed over 72 hours with SCLC cell lines H526 (A), H146 (B), WBA (C), and H209 (D) in complete medium and increasing concentrations of NVP-ADW742 and carboplatin. Data is displayed as a percentage of control growth, with a negative value indicating net cytotoxicity. The CI, as calculated using the Chou-Talalay equation, is displayed within each graph. Data from at least three individual experiments; points, mean of eight replicate wells; bars, ±SE.
DISCUSSION

We have shown that inhibition of IGF-I signaling with the small molecular mass IGF-IR kinase inhibitor NVP-ADW742 enhances the sensitivity of SCLC cell lines to etoposide and carboplatin in a synergistic fashion. The rationale for performing this series of experiments was based on our observation that partial inhibition of PI3K-Akt signaling by the PI3K inhibitor LY294002 produced marked chemosensitization in SCLC cell lines (25). Because IGF-I is the predominant activator of PI3K-Akt signaling in SCLC cell lines, we reasoned that IGF-IR kinase inhibition could also sensitize these cell lines to chemotherapy by the same mechanism. This seems to be the case because the maximal response to the combination of the cytotoxic drugs with NVP-ADW742 occurred at compound concentrations that markedly reduced or eliminated basal Akt activity (Fig. 1). In the WBA cell line, in which significant Akt activity remained at the maximal selective concentration of NVP-ADW742, the addition of imatinib, which further reduced Akt activity in this setting, further enhanced sensitivity to etoposide (Fig. 4). Thus, in lieu of specific tolerable inhibitors of PI3K-Akt signaling, targeting of growth factor receptors responsible for activating this pathway, such as the IGF-IR and c-Kit in SCLC, seems to be a potentially useful therapeutic strategy for enhancing the efficacy of chemotherapeutic agents. This effect is in addition to the antiproliferative and proapoptotic effects of combining imatinib with NVP-ADW742 (Fig. 4; ref. 24).

Given these results and those of our previous study (24), a potential explanation for the inactivity of single agent imatinib in the treatment of SCLC is apparent (32, 33). If sufficient IGF-I is present as a result of either autocrine or paracrine/endocrine production, the effect of c-Kit inhibition on PI3K-Akt activity would likely be limited and therefore so would effects on growth and apoptosis. However, because partial inhibition of PI3K-Akt activity is sufficient to sensitize SCLC cells to chemotherapy (25), it is still possible that imatinib alone may enhance the activity of chemotherapeutic agents against some tumors. This hypothesis is being tested in ongoing clinical trials (34). However, it is likely, based on the data presented in Fig. 4, that for optimal chemosensitization across the broadest range of tumors, the combination of c-Kit and IGF-IR inhibition will be necessary.
Our results are consistent with a large body of evidence which suggests that IGF-I signaling results in chemotherapy resistance in a wide variety of tumors (35). For instance, IGF-I induced resistance of breast cancer cell lines to a variety of cytotoxic agents including paclitaxel (36, 37) and inhibition of IGF-IR signaling using a monoclonal antibody (38) or expression of a dominant-negative mutant of the IGF-IR (39) enhanced sensitivity to paclitaxel. An anti-IGF-IR antibody enhanced the sensitivity of pancreatic cancer xenografts to gemcitabine (40) and antisense inhibition of IGF-IR enhanced sensitivity of prostate cancer cells to cisplatin, mitoxantrone, and paclitaxel (41). Also utilizing NVP-ADW742, Mitsiades et al. (23) have shown that IGF-IR kinase inhibition enhances the sensitivity of multiple myeloma cells to melphalan, doxorubicin, and bortezomib. The effects on melphalan sensitivity were seen both in vitro and in a multiple myeloma xenograft model. They also showed a 2- to 4-fold reduction in HIF-1α DNA binding activity and VEGF secretion by myeloma cells treated with NVP-ADW742, which is consistent with our observed reductions in VEGF mRNA and protein expression in SCLC cell lines. The latter observations suggest that NVP-ADW742 and the related IGF-IR kinase inhibitor NVP-AEW541 (22) could serve as potent antiangiogenic agents.

Given their ability to inhibit tumor cell growth, induce sensitization to the apoptotic effects of chemotherapy, and reduce expression of angiogenic growth factors, the pyrrolo(2,3-d)pyrimidine class of IGF-IR kinase inhibitors (22) would seem to be ideal agents for the treatment of tumors dependent on IGF/IGF-IR signaling. One concern with targeting IGF-IR kinase activity is the potential for cross-inhibition of the highly homologous insulin receptor. NVP-ADW742 and NVP-AEW541 have >16- and 26-fold selectivity, respectively, for the IGF-IR versus the insulin receptor in cellular autophosphorylation assays. At doses that effectively inhibited IGF-IR kinase activity, neither compound had any significant effect on body weight, blood glucose, or insulin levels in treated mice, which should be sensitive indicators of the metabolic effects of insulin receptor inhibition (22, 23). This issue will continue to be a concern, however, as these or other IGF-IR kinase inhibitors progress through preclinical testing and into clinical trials. Given the potential for the effectiveness of IGF-IR signaling inhibitors in cancer treatment, it is important to also recognize that several clinically viable alternative approaches exist. There are non-ATP site-directed competitive IGF-IR kinase inhibitors under development (42, 43), as well as a variety of anti-IGF-IR antibodies (40, 44, 45). Given that the side effect profile of these agents is likely to be different, the expectation that modulators of IGF-IR activity will progress to later stage clinical trials seems high.

Based on observations made in this and a previous study (24) several conclusions could be drawn concerning the utilization of IGF-IR kinase inhibitors in the treatment of SCLC. First, for them to be effective as single agents in SCLC, they must significantly decrease Akt activity in tumor cells. To achieve this in some tumors, it may be necessary to add a c-Kit kinase inhibitor (e.g., imatinib) because c-Kit can maintain Akt activity in some tumor cell lines and dual inhibition of IGF-IR and c-Kit is synergistic in this setting. Thus, one important pharmacodynamic end-point in a trial of an IGF-IR kinase inhibitor in SCLC should be a significant decrease in Akt activity within the tumor. The present study also documents that maximal synergy with etoposide and carboplatin...
would be expected at the same pharmacodynamic end-point. Based on our demonstration that NVP-ADW742 in combination with chemotherapy synergistically inhibits growth, induces apoptosis, and reduces VEGF expression, we believe that IGF-IR kinase inhibitors could have an important role in the future therapy of SCLC.

REFERENCES
