SKI-606, a Src/Abl Inhibitor with In vivo Activity in Colon Tumor Xenograft Models

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Abstract

Src up-regulation is a common event in human cancers. In colorectal cancer, increased Src levels are an indicator of poor prognosis, and progression to metastatic disease is associated with substantial increases in Src activity. Therefore, we examined the activity of SKI-606, a potent inhibitor of Src and Abl kinases, against colon tumor lines in vitro and in s.c. tumor xenograft models. SKI-606 inhibited Src autophosphorylation with an IC50 of ~0.25 μmol/L in HT29 cells. Phosphorylation of Tyr418 in HT29 and Colo205 spheroids was reduced by similar concentrations of inhibitor. Antiproliferative activity on plastic did not correlate with Src inhibition in either HT29 or Colo205 cells (IC50s, 1.5 and 2.5 μmol/L, respectively), although submicromolar concentrations of SKI-606 inhibited HT29 cell colony formation in soft agar. SKI-606 also caused loosely aggregated Colo205 spheroids to condense into compact spheroids. On oral administration to nude mice at the lowest efficacious dose, SKI-606 caused loosely aggregated Colo205 spheroids to condense into compact spheroids. On oral administration to nude mice at the lowest efficacious dose, SKI-606 also caused twice daily administration was necessary to inhibit Colo205, whereas once daily administration of SKI-606 inhibited HT29 tumor growth. These results support development of SKI-606 as a therapeutic agent for treatment of colorectal cancer.

Note: J.M. Golas and J. Lucas contributed equally to this work.

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Introduction

Epidemiologic evidence indicates that up-regulation of levels and activity of the nonreceptor protein tyrosine kinase c-Src is associated with colon tumor progression (1–3). Although modest increases in Src levels or activity occur early in tumor development, disease progression is accompanied by further increases in Src expression and activity, such that total Src activity in metastatic colorectal tumors can be as high as 90 times that found in normal mucosa (4, 5). Furthermore, increases in Src activity as small as 2.2-fold relative to normal mucosa are associated with poor prognosis in colorectal cancer patients (6). These observations suggest that Src is an attractive target for therapeutic intervention in colorectal cancer.

Src is implicated in other cancers besides those of colorectal origin, as it is overexpressed in the majority of breast and non–small cell lung cancers (1, 7). A more limited sampling of pancreatic and ovarian cancers indicate that Src activation is likely to be prevalent in these diseases as well (8–10). Numerous laboratory studies suggest that Src activation induces phenotypic traits associated with metastatic cells, such as increased cell motility, invasiveness, and survival (11–22). Additionally, antisense Src diminishes vascular endothelial growth factor (VEGF) up-regulation in HT29 cells incubated under hypoxic conditions, reduces vascularization in HT29 tumors, and inhibits growth of HT29 colon and SKOV-3 ovarian tumor xenografts (23–25). Host deficiency in either Src or the highly related family member Yes reduced tumor cell extravasation and metastatic burden in a lung metastasis model, with inhibition of vascular endothelial cell permeability a likely mechanism (26). Pharmacologic intervention with Src inhibitors against nude mouse s.c. tumors has not always been successful, but PP2, an inhibitor of Src family kinases, was effective in a liver metastatic HT29 tumor model (27–29). Concomitant administration of gemcitabine and PP2 or the Src inhibitor AZM475271 ablated growth of pancreatic tumor xenografts in orthotopic models, whereas other Src inhibitors caused significant inhibition of osteolytic bone metastases in a murine model (30–32). These findings are consistent with the epidemiologic evidence suggesting an increasing role for Src with increasing malignancy (see ref. 1 for a review).

In an earlier report, we described a selective Src inhibitor with in vivo activity against Src-transformed fibroblast xenografts (33). In that article, we reported that this compound, SKI-606, does not inhibit receptors for platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and insulin-like growth factor-I (IGF-I) and is only weakly active against Her-2. SKI-606 was subsequently shown to be a potent Abl tyrosine kinase inhibitor that is orally active in a K562 chronic myeloid leukemia (CML) model (34). We also reported that SKI-606 inhibited growth of HT29 colon tumor xenografts in nude mice but that a narrow therapeutic window was observed (33). Others have reported that i.p. administration of SKI-606 inhibits tumor cell extravasation probably by blocking Src activation on stimulation of the VEGF receptor Flk-1 (26). In this report, we show an improved therapeutic window with oral administration, oral pharmacokinetic characterization, efficacy in additional xenograft models, and characterization of SKI-606 biochemical activity in tumor cells and tumor xenografts.

Materials and Methods

Cell culture. HT29, Colo205, DLD1, and HCT116 cells were obtained from American Type Culture Collection (Rockville, MD). Cells were cultured in RPMI 1640 supplemented with 10% FCS, nonessential amino acids,
glutamine, and gentamicin (50 μg/mL; all reagents from Invitrogen, Carlsbad, CA). Cell proliferation was measured in a 96-well format. Cells were plated on day 1 (2,000 per well). On day 2, SKI-606 was added in a small volume from a stock in RPMI 1640 supplemented with FCS and DMSO such that the final concentration of DMSO did not exceed 0.1%. Cell-Glo reagent (Promega, Madison, WI) was added on day 5 to determine relative cell number.

Growth in soft agar was determined by plating 500 cells per well in a six-well dish in 3 mL medium with 0.4% agar (Invitrogen) as an overlay on a surface of in 0.8% agar with 4 mL medium. Compound was added to the top agar before pouring to give the desired concentration after complete equilibration with the bottom agar. Liquid medium (1 mL) containing compound at the desired final concentration was added the day after plating the top agar. The agar experiments were also done under conditions where compound was included in the bottom agar and top agar at the desired final concentration. Identical results were obtained with the two methods. The experiments reported here were done with HT29 cells from American Type Culture Collection after either three or four passages (obtained in 2003). Colony-forming assays were done by plating 200 or 500 cells per well in a six-well dish with compound present in the plating medium to mimic the conditions used in the soft agar colony formation experiments. After 5 days, colonies were stained with crystal violet and counted with the aid of a stereomicroscope. Determination of the proliferation of spheroids was described previously (35). Briefly, tumor cells (4 × 10^5) were suspended in 5 mL culture medium and seeded in a Petri dish or on a 0.5 mL underlayer of 0.66% agar. Spheroids were allowed to form over a 4-day period after which spheroids with a diameter of ~0.15 mm were selected and transferred to a 24-well dish containing 0.5 mL culture medium. The two perpendicular diameters of each spheroid were measured at the time of replating and at the indicated intervals over a period of 6 days. The diameters were measured with the aid of a calibrated reticle mounted in the ocular of a stereoscope.

**Antibodies.** Monoclonal antibodies GD-11 to Src, 4G10 to phosphoryl-rhoosine, and rabbit polyclonal antibody to focal adhesion kinase (FAK) were purchased from Upstate Biotechnology (Lake Placid, NY). Antibodies to PY418 Src, PY397, PY925, and PY861 FAK were purchased from Biosource (Camarillo, CA). Antibody to actin was purchased from Chemicon (Temecula, CA). The total Src and PY418 Src ELISA kits were purchased from Biosource.

**Biochemical analysis.** Compound was diluted from a stock solution in DMSO directly into medium. The same volume of DMSO was added to medium in the mock-treated samples (final DMSO concentration did not exceed 0.1%). Cells were exposed to compound for 4 hours, unless otherwise indicated, and lysed with lithium dodecyl sulfate sample buffer (Invitrogen), radioimmunoprecipitation assay (RIPA) buffer [20 mmol/L Tris-HCl (pH 7.5, room temperature), 0.1 mol/L NaCl, 1 mmol/L EDTA, 1% NP40, 0.5% sodium deoxycholate], or urea lysis buffer [50 mmol/L Tris-HCl (pH 7.5, room temperature), 7 mol/L urea, 1 mmol/L EDTA, 0.1% SDS]. Samples were analyzed by gel electrophoresis and blotted to nitrocellulose or polyvinyldiene difluoride membrane. Protein loading was adjusted by relative cell number or by protein determination, and equal loading was verified by probing blots with antibody to actin. Protein concentrations were determined with Bradford reagent, DC reagent (Bio-Rad, Hercules, CA), or BCA reagent (Pierce, Rockford, IL) either directly or after treatment with Compat-Able Protein assay kit (Pierce) with bovine IgG (Bio-Rad) as a standard. The Src and PY418 Src ELISA kits were purchased from Biosource and were used according to the manufacturer’s specifications.

**In vivo studies.** All animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol. Tumor cells were suspended to 50 million cells/mL and the cell suspension (0.2 mL) was injected s.c. into a flank of 6 to 7 weeks old female nude mice (Charles River, Wilmington, MA). Mice with tumors larger than 200 mm^3 after 1 week were given vehicle or compound by oral gavage at the indicated doses in 0.2 mL vehicle containing 0.5% methylcellulose and 0.4% polysorbate 80 (Tween 80). Pharmacokinetic measurements were done with fed female nude mice given an oral gavage as above. Blood was drawn by cardiac puncture from euthanized animals. Samples were analyzed as described in Boscelli et al. (33).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Characterization of SKI-606 activity against HT29 cells in culture. A, HT29 cells were plated and treated with SKI-606 as described in Materials and Methods. Points, mean of six separate determinations. Bars, SD. B, dose response of HT29 cell growth in soft agar. All visible colonies were counted regardless of size. Points, average of four determinations; bars, SD. C, effect of SKI-606 on colony formation under clonogenic conditions. HT29 cells were plated in the presence of the indicated concentration of SKI-606 as described in Materials and Methods. Colonies were stained with crystal violet and counted after 7 days. Points, average of four determinations; bars, SD. D, effect of SKI-606 on HT29 spheroid growth. Spheroids were collected as described in Materials and Methods and their size was determined on day 0. SKI-606 was added on day 0 and spheroid volume was measured on day 6. Ten spheroids were measured for each data point. Bars, SD.
Results

Effects of SKI-606 treatment on tumor cells in culture. SKI-606 inhibits anchorage-independent growth of rat fibroblasts transformed with activated Src with an IC$_{50}$ of 100 nmol/L, with corresponding inhibition of Src-dependent phosphorylation of cellular proteins (33). In contrast, SKI-606 inhibited the proliferation of HT29 tumor cells on tissue culture plates with an IC$_{50}$ of 1.5 µmol/L, significantly above the IC$_{50}$ for inhibiting growth of the Src fibroblasts in suspension (Fig. 1A). This value is lower than the 5 µmol/L value reported in our earlier article because of the lower cell densities used for the assays in this study.

We reported previously that SKI-606 inhibited HT29 cell colony formation in agar (33). A more quantitative analysis shown here (Fig. 1B) indicates that colony formation in agar was inhibited with an IC$_{50}$ of 0.4 µmol/L. Because colony formation in soft agar was measured with cells plated in the presence of compound, it was possible that SKI-606 was inimical to the survival of single cells, whether growing in suspension or attached on plastic. To assess this possibility, we compared the plating efficiency of HT29 cells in the presence and absence of SKI-606 and found that treatment with compound reduced both the number of colonies and the colony size. The resultant IC$_{50}$ for inhibiting colony formation (defined as a colony visible by eye) was ~1.5 µmol/L (Fig. 1C), roughly thrice higher than observed for growth in suspension and identical to the IC$_{50}$ determined in the 96-well proliferation assays. These results suggest that attachment on plastic provided a modest survival benefit against SKI-606 treatment that is absent in cells growing in suspension in soft agar, consistent with the results of Windham et al., where other Src inhibitors caused increased apoptosis in HT29 cells forced to grow in suspension (19). We also examined whether cell-cell interactions provided any protection against exposure to SKI-606 by examining the effect of SKI-606 on spheroid growth of the American Type Culture Collection HT29 cells. As shown in Fig. 2A, SKI-606 inhibited spheroid growth with an IC$_{50}$ of ~2.5 µmol/L. The decreased sensitivity of HT29 spheroid growth to SKI-606 treatment compared with the cells growing in agar suggests that cell-cell interactions protect against SKI-606 treatment.

We then studied the effect of SKI-606 on the proliferation of Colo205 cells, another colorectal tumor line, which expresses Src at approximately half the levels present in HT29 cells (7). As shown in Fig. 2A, SKI-606 reduced the proliferation of these cells on plastic (IC$_{50}$, 2.5 µmol/L). The effect of SKI-606 on Colo205 cell growth in soft agar was not studied in detail because these cells degraded the agar matrix during the study (3-4 weeks). However, SKI-606 had a pronounced effect on the appearance of Colo205 spheroids (Fig. 2B). Before addition of compound, the Colo205 spheroids consisted of a loosely aggregated clump of cells in which individual cells could be readily distinguished (Fig. 2B, left). Within 4 hours of addition of SKI-606, this loose aggregate condensed into a dense ball with no discernible cell boundaries (Fig. 2B, middle). The spheroid maintained this appearance for the duration of the study. To determine the effect of a cytotoxic agent on the spheroid, the DNA-damaging agent calicheamicin was added. Calicheamicin reduced the total cell number and disrupted the spheroid (Fig. 2B, right). Spheroid size was significantly reduced by SKI-606 in a dose-dependent manner in a 6-day experiment (Fig. 2C), but note that spheroid size probably bears no direct relationship to the cell number. These observations suggest that SKI-606 strengthens cell-cell interactions in this line, a hypothesis consistent with the role of Src in regulating cell-cell adhesion (11, 13, 14, 29).

Figure 2. Effect of SKI-606 on Colo205 spheroids. A, spheroid size after 6-day exposure to different concentrations of SKI-606. B, photomicrographs of representative Colo205 spheroids after 3-day exposure to no compound (0.1% DMSO; left), SKI-606 (1.66 µmol/L; middle), or the cytotoxic agent calicheamicin (33.3 nmol/L; right). C, spheroid size at various times of exposure to no compound (●) or 1.66 µmol/L (▲), 3.33 µmol/L (▲), and 5 µmol/L (●) SKI-606.

Inhibition of Src and Src target protein phosphorylation by SKI-606. To define the effect of SKI-606 treatment on Src activity in the HT29 and Colo205 tumor lines, we examined Src phosphorylation on Y418 and Src-dependent phosphorylation of the downstream Src substrate FAK. Phosphorylation of Y418 increases Src activity and is generally viewed as an autophosphorylation reaction, although another cellular kinase seems capable of phosphorylating this residue (36). In spite of this possible ambiguity, Y418 phosphorylation is certainly an indicator of Src activation. Therefore, we examined Src phosphorylation on Y418 in extracts of HT29 and Colo205 cells incubated with SKI-606 for 4 hours. We observed a similar dose-dependent decrease in phosphorylation of Y418 in the two colon tumor lines, where Y418 phosphorylation was nearly ablated by 1 µmol/L SKI-606 (Fig. 3A, top, HT29 cells, and bottom, Colo205 cells). A quantitative evaluation was done with the aid of a sandwich ELISA assay. In this assay, SKI-606 reduced Src phosphorylation on Y418 with an IC$_{50}$ of ~250 nmol/L when measured in this manner, consistent with the immunoblot results (Fig. 3B).

To examine inhibition of phosphorylation of downstream targets, we chose FAK in view of its central role in coordinating adhesion and growth factor signaling (37). FAK phosphorylated on its autophosphorylation site Y397 acts as a docking site for Src. Association of Src with Y397 activates Src, after which Src phosphorylates Y576, Y577, Y861, and Y925 in FAK (38-42). The effect of SKI-606 on
phosphorylation of Y861 and Y925 in HT29 and Colo205 cells is shown in Fig. 3C and D. Y925 phosphorylation decreased following treatment with SKI-606 (IC50 ~ 200 nmol/L by densitometry) and was almost completely ablated by 1 μmol/L SKI-606 in both cell lines, whereas Y397 phosphorylation in the HT29 line was unaffected by 1 μmol/L SKI-606 (Fig. 3C, bottom). In contrast to Y925, significant phosphorylation of Y861 was observed in extracts from both cell lines after treatment with 1 μmol/L SKI-606 (Fig. 3C and D). Because Y397 phosphorylation was unaffected by 1 μmol/L SKI-606, reduced phosphorylation of FAK Y925 does not reflect inhibition of FAK itself but coincides with a reduction in Src activity.

Pharmacokinetic properties of orally given SKI-606. SKI-606 plasma levels in the nude mouse following i.p. administration were reported earlier (33). For development of SKI-606 as an orally given agent, pharmacokinetic studies were done to support the oral xenograft studies. As shown in Table 1, peak plasma concentrations of ~3 μmol/L were observed after administration of a 50 mg/kg dose of SKI-606. The trough plasma level of SKI-606 was ~90 nmol/L at this dose. The peak plasma level of SKI-606 was not significantly increased by oral administration of 150 mg/kg compound, whereas trough plasma levels increased to ~350 nmol/L. These results suggested that SKI-606 plasma levels attained with oral dosing were adequate to inhibit Src kinase activity in vivo. Further pharmacokinetic characterization indicated that SKI-606 had a bioavailability of 18% with a t1/2 of 8.6 hours and a large volume of distribution (18 L/kg).

Inhibition of tumor growth by SKI-606. The ability of SKI-606 to inhibit the growth of HT29 and Colo205 s.c. xenograft tumors was examined. In HT29 xenograft studies, SKI-606 was given by oral gavage once daily to mice with tumors ranging from 200 to 300 mg. As shown in Fig. 4A, a dose-dependent antitumor response was observed in those mice given doses of 25 to 150 mg/kg over a 21-day period (P < 0.003 in Student’s two-tailed t test in the group that received the 25 mg/kg/d). Although the once daily 25 mg/kg dose was not consistently active, the higher doses were reproducibly effective. No deaths occurred and no weight loss was observed in animals given SKI-606 at 150 mg/kg. The toxicity observed in our earlier studies may have been due to the use of a different vehicle in conjunction with twice daily dosing (33).

Table 1. Plasma levels of SKI-606 after oral administration at 50 and 150 mg/kg

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Time (h)</th>
<th>Plasma levels (SD), μmol/L</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>0.5</td>
<td>0.79 (0.06)</td>
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<tr>
<td></td>
<td>2</td>
<td>2.74 (0.56)</td>
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<tr>
<td></td>
<td>4</td>
<td>2.50 (1.19)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.09 (0.04)</td>
</tr>
<tr>
<td>150</td>
<td>3</td>
<td>3.33 (0.51)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2.17 (0.81)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.35 (0.17)</td>
</tr>
</tbody>
</table>

NOTE: Three animals per group were dosed as described in Materials and Methods.
In contrast to HT29 xenograft studies in which once daily administration of SKI-606 was efficacious, twice daily administration of SKI-606 was necessary to inhibit growth of Colo205 xenografts (Fig. 4B). Significant antitumor activity was observed with twice daily doses of 75 mg/kg for 10 days (doses spaced 12 hours apart). Increasing the dose had no additional benefit, whereas 50 mg/kg twice daily was inactive. The antitumor activity of the twice daily 75 mg/kg dose, although modest, was statistically significant ($P < 0.003$) and highly reproducible. Similar results were obtained with DLD1 and HCT116 xenografts when SKI-606 was given orally at 100 mg/kg twice daily for 21 consecutive days. In these experiments, the second dose was given 10 hours after the first dose of the day (Fig. 4C and D, respectively; $P < 0.01$ in both cases). No weight loss or compound-related animal deaths occurred in these studies.

**Inhibition of Src phosphorylation in tumor xenografts.** We next examined the effect of compound administration on Src activation in HT29 tumors in nude mice. An oral gavage of SKI-606 (150 mg/kg) on day 1 was given to the mice and tumors were excised 24 hours later. Two other groups were given a second 150 mg/kg dose on day 2 (at 24 hours after the first dose) and tumors were excised 3 and 6 hours after this second administration. Extracts from these tumors were analyzed for Src levels and for Src phosphorylation on Y418 by immunoblot and ELISA assay. As shown in the immunoblot of Fig. 5A, there was a significant decrease in Src phosphorylation (top band) at all time points. The additional bands migrating below Src that also disappear upon compound treatment may represent phosphorylated forms of other Src family kinases present in the mouse blood carried over with the tumor sample. We also examined Src phosphorylation on Y418 using the Biosource ELISA assay (Fig. 5B). Greater than 50% inhibition of Y418 phosphorylation were observed at 24 hours after the first dose, with a more complete reduction occurring at 3 and 6 hours after the second dose. Significant inhibition of Src autophosphorylation was also observed in the Colo205 xenografts (Fig. 5C). In this experiment, SKI-606 was given by oral gavage at 75 mg/kg b.i.d., and tumors were excised 24 hours after the first dose. These results are consistent with pharmacokinetic data shown in Table 1.

**Discussion**

SKI-606 is a potent Src kinase inhibitor that blocks Src autophosphorylation and the phosphorylation of downstream target proteins at submicromolar concentrations in all cells examined. Although the antiproliferative activity of SKI-606 does not directly

![Figure 4](image-url)
tumor xenografts of SKI-606-treated animals under conditions where antitumor activity was observed.

SKI-606 inhibits Abl as well as Src family nonreceptor tyrosine kinases and is active in vivo against Src-transformed fibroblasts and K562 CML xenografts (33, 34, 43). Its activity against K562 tumors is likely due to inhibition of the tyrosine kinase activity of Bcr-Abl, although the ability of SKI-606 to inhibit Src family kinases may also be physiologically significant in this model. The Abl inhibitor imatinib has marginal activity against HT29 xenografts, an activity ascribed to the additional activity of imatinib against the receptor tyrosine kinase c-Kit (44). However, it is possible that Abl inhibition was also a factor in that study; therefore, the ability of SKI-606 to inhibit Abl might contribute to its in vivo activity against colon tumor xenografts. We note that SKI-606 does not possess pharmacologically significant activity against several other kinases, including PDGF receptor, FGF receptor, Her-2, epidermal growth factor receptor (EGFR), IGF-1 receptor, KDR (Flk-1), protein kinase A, protein kinase C, I KK, Cdk4, p38, and S6K (33).

SKI-606 has less obvious effects on the tumor lines in this study than observed for EGFR or Abl tyrosine kinase inhibitors now in the clinic, where antiproliferative activity consistent with inhibition of biochemical activity of those kinases was reported (45–47). Other investigators failed to find any correlation between Src expression and response to their potent Src inhibitors in proliferation assays in culture or in vivo (28, 48). However, Src inhibitors besides SKI-606 block anchorage-independent growth of HT29 cells and those compounds were also less effective in blocking proliferation on plastic, perhaps reflecting increased Src activity in tumor cells kept in suspension (49, 50). Because SKI-606 reduces VEGF-mediated vascular permeability and tumor cell extravasation, the effect of Src inhibition on stromal cells, as well as on other tumor-host interactions, may be critical determinants for in vivo efficacy. It is perhaps significant that both epidemiologic and laboratory evidence suggests an important role for Src in metastatic cancer. SKI-606 activity in the s.c. xenografts presented here is modest compared with the striking results reported for PP2 in the metastasis model (29). Although work is in progress to define SKI-606 activity in this and other metastatic tumor models, the clinic remains the definitive test of the efficacy of this molecule.

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References


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