Molecular Imaging of Post-Src Inhibition Tumor Signatures for Guiding Dasatinib Combination Therapy

Liquan Gao*1, Hao Liu*1, Xianlei Sun1, Duo Gao1, Chenran Zhang1, Bing Jia1, Zhaohui Zhu2, Fan Wang1,3, and Zhaofei Liu1

1Medical Isotopes Research Center and Department of Radiation Medicine, School of Basic Medical Sciences, Peking University Health Science Center, Beijing, China; 2Department of Nuclear Medicine, Peking Union Medical College Hospital, Beijing, China; and 3Interdisciplinary Laboratory, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

Noninvasive, real-time, quantitative measurement of key biomarkers associated with cancer therapeutic interventions could provide a better understanding of cancer biology. We investigated in this study whether incorporating multiple molecular imaging approaches could be used to guide dasatinib anti-Src therapy and aid in the rational design of a combination therapy regimen. Methods: Bioluminescence imaging, 18F-FDG PET, integrin αvβ3-targeted SPECT/CT, and vascular endothelial growth factor–targeted near-infrared fluorescence imaging were performed before and after dasatinib treatment in a tumor mouse model. Results: There was no significant difference in the bioluminescence imaging signal or 18F-FDG tumor uptake in dasatinib-treated tumors compared with the control tumors. However, the uptake of 99mTc-3PRGD2 (integrin αvβ3–specific) and DyLight755-ranibizumab (vascular endothelial growth factor–specific) in the dasatinib-treated tumors was significantly lower than that in the control tumors. In vitro studies confirmed the antiangiogenic effects of dasatinib but indicated a lack of cytotoxicity. Dasatinib plus docetaxel docetaxel elicited marked synergistic tumor growth inhibition in vivo. Conclusion: Visualization of post-Src-inhibition tumor signatures through multiple imaging approaches facilitates sensitive and quantitative measurement of cancer biomarkers in vivo, thus aiding in the rational design of dasatinib combination therapy.

Key Words: image-guided therapy; angiogenesis; tumor response; dasatinib; Src family of kinases

DOI: 10.2967/jnumed.115.158881

T he Src family kinases (SFKs) are a large family of nonreceptor protein tyrosine kinases, which regulate numerous intracellular signaling pathways responsible for tumor cell proliferation, invasion, angiogenesis, and metastasis (1). SFK activity is upregulated in many malignant tumor types, thus representing a promising target for tumor therapy (2). Dasatinib (BMS-354825) is an orally bioavailable small-molecule Src inhibitor that has been approved for chronic myelogenous leukemia and is being extensively studied in both preclinical and clinical studies as a promising agent for the management of various solid tumors (1,2).

Despite significant progresses in dasatinib-based Src-targeted therapy, many tumors relapse after an initial response and become refractory to therapy, consequently leading to treatment failure. To overcome dasatinib resistance, numerous combination therapeutic regimens have been evaluated. Although promising in some cases, several studies have demonstrated the failure of dasatinib combination therapy or reported controversial outcomes. One study in 2 patients with castration-resistant prostate cancer showed that dasatinib plus docetaxel (DTX) provided meaningful clinical benefits and delayed disease progression (3). However, in a randomized, double-blind phase 3 trial in patients with castration-resistant prostate cancer, dasatinib plus DTX was not found to improve overall survival or to improve any measures of patient benefit (4); these results highlight the importance of a rational design of a combination therapy regimen toward personalized cancer treatment.

A critical step in personalized cancer therapy is the development of effective noninvasive in vivo imaging techniques for predicting or monitoring tumor response at the earliest stages. However, single-modality imaging is not sufficient for assessing the multiple molecular signatures of some cancers. Integration of various noninvasive imaging modalities gives a readout of multiple cancer biomarkers, thus providing complementary information at a functional and anatomic level (5).

Several molecular imaging probes have been investigated for noninvasively monitoring tumor responses to therapies. For example, 18F-FDG PET is commonly used in the clinical setting for visualization of tumor glucose metabolism in vivo (6). Integrin αvβ3 is overexpressed in numerous tumor cells and activated endothelial cells during tumor angiogenesis. SPECT imaging using 99mTc-3PRGD2 (7), a 99mTc-labeled arginine-glycine-aspartic acid (RGD)–based radiotracer, has been used to visualize and quantify tumor integrin αvβ3 expression in vivo. Further, vascular endothelial growth factor (VEGF) is a key inducer of tumor angiogenesis. Recent studies have demonstrated that near-infrared fluorescence (NIRF) dye-labeled anti-VEGF antibodies can specifically detect changes in VEGF in response to cancer therapies (8–10).

In this study, to visualize several different tumor signatures with high contrast and specificity, we performed bioluminescence imaging (BLI), 18F-FDG PET, integrin αvβ3 SPECT, and VEGF-targeted NIRF imaging, simultaneously, in a human lung cancer mouse model treated with dasatinib. Noninvasive multiparameter imaging enabled the in vivo detection of early tumor changes during dasatinib therapy,
and the data obtained facilitated the rational design of a more efficacious strategy for dasatinib combination therapy.

**MATERIALS AND METHODS**

**Cell Culture and Animal Model**

The A549 human non–small cell lung cancer cell line was obtained from American Type Culture Collection. Firefly luciferase stably transfected A549 (A549-fLuc) cells were generated using a previously described method (11). A robust linear correlation between the A549-fLuc cell number and fLuc activity was observed ($R^2 = 0.9915, P < 0.0001$; Supplemental Figs. 1A and 1B [supplemental materials are available at http://jnm.snmjournals.org]), and no significant difference between A549 and A549-fLuc cells was observed in terms of proliferation (Supplemental Fig. 1C).

All animal experiments were performed in accordance with the Guidelines of Peking University Animal Care and Use Committee. The A549-fLuc subcutaneous tumor model was established as described in the supplemental materials and methods.

**In Vivo Dasatinib Treatment**

A549-fLuc tumor–bearing BALB/c nude mice with a tumor size of 150–200 mm$^3$ were segregated into 6 groups: BLI/NIRF imaging control ($n = 7$), BLI/NIRF imaging treatment ($n = 7$), PET control ($n = 5$), PET treatment ($n = 5$), SPECT control ($n = 5$), and SPECT treatment ($n = 5$). A maximum-tolerated dose of 80 mg/kg/d for dasatinib (6 d of continuous administration) was determined in our pilot study, and 50% of the maximum tolerated dose was used in this study. After the baseline imaging (day 0), animals in the treatment groups were administered dasatinib (40 mg/kg/d) (in 1:1 propylene glycol/water) via gavage for 6 d (days 1–6). Animals in the control groups were administered 1:1 propylene glycol/water (vehicle control) using the same protocol. Molecular imaging was repeated on day 7 (the schedule of dasatinib treatment and imaging are shown in Fig. 1A). Immediately after the imaging studies, animals in the PET control and treatment and SPECT control and treatment groups were sacrificed. The tumors were harvested, immediately frozen in optimal cutting temperature medium, and then cut into 5-μm-thick slices for immunofluorescence staining. The tumor size in the BLI/NIRF control and BLI/NIRF treatment groups was measured every 4 d to observe the effect of dasatinib on the tumor growth.

**BLI**

Detailed procedures of BLI are described in the supplemental materials and methods. The BLI signal intensity in the tumor regions was quantified as the sum of all detected photon counts within the region of interest after subtraction of background luminescence.

**18F-FDG PET**

18F-FDG PET scans and image analysis were performed using a microPET R4 rodent model scanner (Siemens Medical Solutions) as previously described (12,13). Each A549-fLuc tumor–bearing mouse was intravenously injected with 3.7 MBq of 18F-FDG, and 5-min static PET scans were acquired at 1 h after injection. Images were reconstructed, and the region-of-interest–derived tumor percentage injected dose per gram was determined.

**99mTc-3PRGD2 SPECT/CT**

The integrin αvβ3–targeting SPECT radiotracer $^{99m}$Tc-3PRGD2 was prepared as previously described (7). Each A549-fLuc tumor–bearing nude mouse was intravenously administered 18.5 MBq of $^{99m}$Tc-3PRGD2. SPECT and helical CT scans of the mice were obtained at 1 h after injection using a small-animal NanoScan SPECT/CT imaging system (Mediso). The region of interest encompassed the tumor and muscle (background), and the tumor-to-muscle radioactivity (counts/mm$^3$) ratio was calculated.

**DyLight755-Ranibizumab (Dye755-Ran) NIRF**

The human VEGF-specific NIRF imaging agent Dye755-Ran was prepared as previously described (9). Each A549-fLuc tumor–bearing nude mouse was intravenously injected with 0.5 nmol of Dye755-Ran. In vivo small-animal NIRF imaging was then performed at 4 h after injection using the IVIS spectrum system (Xenogen). The region of interest was highlighted for each tumor, and the fluorescence intensity was presented as the average radiant efficiency in the unit of (p/s/cm$^2$/sr)/(μW/cm$^2$).

**Immunofluorescence Staining and Analyses**

A549-fLuc tumor tissues were stained and analyzed for glucose transporter 1 (GLUT-1), Ki-67 proliferation marker, human integrin αvβ3, murine integrin β3, and human VEGF. Detailed procedures are described in the supplemental materials and methods.

**Radioligand Binding Assay**

The effect of dasatinib on integrin αvβ3 inactivation was determined using cell radioligand binding assays. Detailed procedures are described in the supplemental materials and methods.

**FIGURE 1.** Dasatinib had no effect on A549-fLuc tumor growth inhibition. (A) Tumor growth curves of A549-fLuc tumor–bearing mice administered vehicle control or dasatinib daily for 6 d ($n = 7$ group). Inset, schedule of dasatinib treatment and molecular imaging experiments. (B) Representative bioluminescence images and tumor BLI signal intensity changes from baseline to after treatment in the A549-fLuc tumor–bearing mice ($n = 7$ group). Arrows indicate locations of tumors.
The antiangiogenic effect of dasatinib was evaluated by Matrigel plug assay. Detailed procedures are described in the supplemental materials and methods.

In Vivo Combination Therapy

Groups (n = 10/group) of A549-fLuc tumor–bearing BALB/c nude mice with 150–200 mm³ tumors were administered dasatinib (40 mg/kg) (in 1:1 propylene glycol/water) daily via gavage for 6 d (days 1–6), with or without intraperitoneal injection of DTX (5 mg/kg) (in 13% ethanol) on days 1, 3, and 5. Animals in the control group (n = 10) were administered 1:1 propylene glycol/water via gavage and injected intraperitoneally with 13% ethanol. On day 7, 5 animals from each group underwent 18F-FDG PET, 99mTc-3PRGD2 SPECT/CT, and Dye755-Ran NIRF imaging using the same procedures as described above. Immediately after the imaging experiments, 3 animals from each group were sacrificed and the tumor tissues were frozen, sectioned, and stained for Ki-67 to determine the tumor cell proliferation.

Statistical Analysis

Quantitative data are expressed as mean ± SD. Means were compared using the Student t test. P values of less than 0.05 were considered statistically significant.

RESULTS

Dasatinib Had No Antitumor Effects in A549-fLuc Tumor Model

As shown in Figure 1A, the tumor growth curve in the dasatinib treatment group was almost identical to that in the control group, suggesting that the antitumor effect of dasatinib was negligible.

BLI and PET Revealed That Dasatinib Had No Effect on Tumor Cell Proliferation

As shown in Figure 1B, there was a significant increase in BLI signal intensity in both control and dasatinib treatment groups as tumors grew between days 0 and 7. The relative tumor BLI signal intensities (posttreatment/baseline ratio) were 4.38 ± 1.33 and 4.83 ± 1.56 (P > 0.05) for the control and dasatinib treatment groups, respectively. These results demonstrated that 6 d of dasatinib treatment did not lead to tumor BLI signal reduction in this model.

Similar to the results of BLI, the 18F-FDG tumor uptake on day 7 was significantly increased in both the control and the dasatinib treatment groups compared with the baseline, as a result of tumor growth. There was no significant change in the relative 18F-FDG tumor uptake (posttreatment/baseline ratio) between the control and treatment groups (1.53 ± 0.14 vs. 1.37 ± 0.26; P > 0.05; Fig. 2A). To validate the in vivo PET imaging observations on tumor cell proliferation, the tumor tissues were stained for GLUT-1 and Ki-67, markers reflecting tumor glucose metabolism and cell DNA synthesis, respectively. We observed that tumors in both the control and the dasatinib treatment groups showed high expression of GLUT-1 and moderate expression of Ki-67 (Supplemental Figs. 2A and 2B). There were no statistical differences in the GLUT-1 and Ki-67 expressions in the A549-fLuc tumors followed by the dasatinib treatment (Fig. 2B).

SPECT/CT Revealed That Dasatinib Showed Antiangiogenic Effects and Could Inactivate Integrin αvβ3

To investigate whether dasatinib had any effects on other tumor signatures such as tumor angiogenesis, we performed small-animal SPECT/CT using an integrin αvβ3–specific radiotracer, 99mTc-3PRGD2.

FIGURE 3. 99mTc-3PRGD2 SPECT/CT imaging revealed decreased murine integrin β3 expression and inactivated integrin αvβ3 after dasatinib treatment. (A and B) Representative small-animal SPECT/CT images (A) and relative tumor 99mTc-3PRGD2 uptake (posttreatment/baseline ratio) (B) in A549-fLuc tumor–bearing mice (n = 5/group). Arrows indicate location of tumors. (C) Quantified human integrin αvβ3 fluorescence intensity and quantified density of murine integrin β3–positive vessels in dasatinib-treated and control A549-fLuc tumor tissues. (D) 125I-c(RGDyK) radioligand binding assay in dasatinib-treated and control A549-fLuc tumor cells. *P < 0.05. ***P < 0.001.
Dasatinib Inhibited Tumor Cell Migration But Had Limited Cellular Toxicity

We observed that dasatinib inhibited the migration of A549-fLuc cells in a dose-dependent manner (Supplemental Figs. 5A and 5B). However, our cell viability studies showed that dasatinib had only a minor effect on cell toxicity. At a high concentration of 1 μM, greater than 80% cell viability was observed (Supplemental Fig. 5C).

Improved Antitumor Effects of Combination Therapy Using Antiangiogenic Dasatinib and Cytotoxic DTX

In contrast to the results observed in the dasatinib treatment group, 10 nM DTX exhibited evident cytotoxicity; the cell viability was less than 50% (Supplemental Fig. 5C). In combination with 30 nM dasatinib, the cytotoxic effect of 10 nM DTX was further increased (Supplemental Fig. 5C). We also performed a cell colony formation assay to confirm the cytotoxicity of DTX. The numbers of cell colonies in the DTX and dasatinib plus DTX groups were significantly fewer than those in the control and dasatinib groups (Supplemental Figs. 5D and SE).

We next assessed the combination of antiangiogenic dasatinib and tumor-cell-toxic DTX in vivo. As shown in Figure 5A, low-dose DTX (5 mg/kg) had a minor effect on tumor growth inhibition, and the combination of dasatinib plus DTX significantly improved this antitumor effect; the tumor size in the dasatinib plus DTX group was significantly smaller than that in the other groups from day 16 up to the end of this study (day 24). Ex vivo Ki-67 staining confirmed that the tumor cell proliferation index (%Ki-67–positive cells) in the dasatinib plus DTX group (10.26 ± 3.88) was significantly lower than that in the control group (37.02 ± 6.26), dasatinib (36.18 ± 7.89), and DTX (21.46 ± 2.89) groups (P < 0.001; Fig. 5B).

Lastly, noninvasive PET, SPECT/CT, and NIRF imaging studies were performed to determine the tumor signatures after dasatinib plus DTX therapy. 18F-FDG PET, 99mTc-3PRGD2, and Dye755-Ran NIRF imaging all demonstrated significantly reduced tumor signals (Fig. 5C; Supplemental Fig. 6).
PET and SPECT are highly sensitive and quantitative and can detect monitoring tumor therapy using 18F-FDG may be confused by solid tumors are perfused with inflammatory cells (cancer biologic markers). Using molecular imaging experiments, (B) Immunofluorescence staining of Ki-67 and quantified percentage of Ki-67-positive cells in A549-Luc tumor tissues harvested from mice treated with vehicle (control), dasatinib (Das), DTX, and dasatinib plus DTX (Das + DTX) daily for 6 d. (C) Quantified tumor uptake (percentage injected dose per gram) of 18F-FDG, tumor-to-muscle ratios of 99mTc-3PRGD2, and tumor fluorescence intensity (radiance efficacy) of Dye755-Ran in A549-Luc tumor-bearing nude mice with or without dasatinib plus docetaxel (Das + DTX) treatment for 6 d (n = 5/group). *P < 0.05. **P < 0.01. ***P < 0.001.

**FIGURE 5.** Significant improvements were observed in vivo antitumor effects when combining dasatinib and DTX. (A) Tumor growth curves of A549-Luc tumor–bearing mice that received vehicle administration of control, dasatinib, DTX, or dasatinib plus DTX (Das + DTX) for 6 d (n = 7/group). Inset, schedule of combination treatment and molecular imaging experiments. (B) Immunofluorescence staining of Ki-67 and quantified percentage of Ki-67–positive cells in A549-Luc tumor tissues harvested from mice treated with vehicle (control), dasatinib (Das), DTX, and dasatinib plus DTX (Das + DTX) daily for 6 d. (C) Quantified tumor uptake (percentage injected dose per gram) of 18F-FDG, tumor-to-muscle ratios of 99mTc-3PRGD2, and tumor fluorescence intensity (radiance efficacy) of Dye755-Ran in A549-Luc tumor–bearing nude mice with or without dasatinib plus docetaxel (Das + DTX) treatment for 6 d (n = 5/group). *P < 0.05. **P < 0.01. ***P < 0.001.

**DISCUSSION**

Cancer therapeutic interventions can lead to multiple changes in the balance and regulation of various signaling pathways, consequently resulting in the upregulation or downregulation of several cancer biologic markers (17,18). Using molecular imaging of different biomarkers, we successfully demonstrated the antiangiogenic effects, but limited cytotoxic effect, of dasatinib in A549-Luc tumors. The information acquired from the imaging studies successfully guided us to conduct combination therapy by simultaneously targeting the tumor cells (using the cytotoxic drug DTX) along with the tumor vasculature (using antiangiogenic dasatinib). This logical regimen led to synergistic efficacy and significantly improved antitumor effect in the A549-Luc mouse model.

Similar to in vivo fluorescence imaging, BLI has the inherent limitation of limited tissue penetration depth. In addition, bioluminescence images are planar and thus may affect data reconstruction and quantification (19). In contrast to optical imaging, PET and SPECT are highly sensitive and quantitative and can detect the therapeutic response earlier than anatomic imaging techniques such as CT. Previous studies (20,21) have demonstrated that 18F-FDG imaging has limitations or is not optimal for monitoring therapeutic tumor response, with one of the major reasons for this finding being that 18F-FDG is not tumor-specific, as it also shows high uptake in benign conditions such as inflammation. Many solid tumors are perfused with inflammatory cells (22,23), and thus monitoring tumor therapy using 18F-FDG may be confused by treatment-induced inflammatory changes (20,21). A previous study demonstrated that dasatinib could inhibit the production of proinflammatory cytokines in vitro (24). However, in this study, dasatinib treatment did not alter the tumor F4/80 levels, a macrophage-specific marker of inflammation (data not shown). Furthermore, both GLUT-1 and Ki-67 staining confirmed that dasatinib treatment did not cause significant changes in tumor glucose metabolic activity or cell proliferation.

Integrin αβ₃–specific RGD radiotracers have been used to monitor tumor responses to several therapeutic drugs and are known to be superior to 18F-FDG for tumor treatment monitoring (21). In most cases, the rationale for RGD radiotracer–based treatment monitoring is that therapies, especially antiangiogenic drugs, can inhibit tumor angiogenesis by downregulating integrin αβ₃ levels, although the detailed mechanism regarding this signaling pathway is not clearly understood. Here we confirmed that dasatinib treatment resulted in downregulation of the host (murine) integrin β3 (expressed on neovasculature). These results, together with the decreased VEGF expression (Fig. 4B) after dasatinib treatment and the reduced blood vessel formation (Fig. 4C) after dasatinib treatment, confirmed the antiangiogenic effects of dasatinib in vivo.

Src family kinases play a critical role for integrin signaling and activation (25), and thus SFK inhibitors (e.g., dasatinib) may cause integrin inactivation. In terms of integrin αβ₃, its binding affinity to endogenous ligands (e.g., vitronectin, fibronectin, and fibrinogen) or synthesized RGD peptides in the inactive state is much lower than that in the activated state (26). Dumont et al. (16) demonstrated that small-animal PET imaging using 64Cu-radiolabeled RGD peptides can specifically detect dasatinib-induced integrin αβ₃ inactivation, thereby allowing monitoring of the tumor responses to dasatinib therapy before any observed changes in tumor size. Imaging using a radiolabeled RGD peptide reflects the tumor response in the dasatinib-responsive U87MG animal model (16); however, in the dasatinib-resistant (Fig. 1A) A549-Luc tumor model, Src inhibition using dasatinib treatment also led to a reduction in the tumor uptake of the radiolabeled RGD peptide (Figs. 3A and 3B). These results suggest that PET or SPECT using radiolabeled RGD peptides is not sufficient to identify whether the tumor is responsive or resistant to dasatinib therapy, which further highlights the merits of multiple tumor signature imaging.

We observed a significantly reduced RGD binding affinity for integrin αβ₃ in the dasatinib-treated tumor cells (Fig. 3D). These results, together with the remarkable effect of dasatinib on the downregulation of murine integrin β3 (Fig. 3C), may be the main reason for the significantly reduced uptake of 99mTc-3PRGD2 in the dasatinib-treated tumors (Figs. 3A and 3B). The antihuman integrin αβ₃ antibody (clone LM609) used for immunofluorescence staining in this study cannot discriminate between low (inactive state)- and high (activated state)-affinity conformations of integrin αβ₃ for RGD (26); therefore, human integrin αβ₃ in the tumor xenografts may be inactivated (low affinity for 99mTc-3PRGD2) after dasatinib treatment, though we did not observe these changes by immunofluorescence staining (Fig. 3C; Supplemental Fig. 3A).

We previously demonstrated that VEGF was a more sensitive biomarker than integrin αβ₃ for antiangiogenic therapy monitoring (8), most likely because VEGF is released from tumor cells into the tumor microenvironment, and, therefore, tumor tissue penetration of the imaging probe is not essential (9). The VEGF NIRF probe (Dye755-Ran) used herein is human VEGF-specific and does not cross-react with murine VEGF (9). Therefore, the host vasculature status after Src inhibition was determined using
the Matrigel plug assay and murine integrin $\beta$3 staining. Dye755-Ran could be simply adapted to produce radiolabeled probes for PET and SPECT by changing the NIRF dye to half-life–matched radionuclides such as $^{89}$Zr and $^{111}$In, which can be used in the clinic. Indeed, VEGF-targeted PET imaging using $^{89}$Zr-labeled antibodies has shown promise for tumor response monitoring in recent clinical trials (27–29).

By using molecular imaging approaches, we demonstrated the antiangiogenic effects and lack of cytotoxic effect of dasatinib. Logically, we hypothesized that, if used in combination with a cytotoxic agent such as DTX, dasatinib would show more effective antitumor efficacy in the dasatinib-resistant A549-ILuc mouse model. The in vivo therapy studies clearly verified the improved efficacy of combining antiangiogenic dasatinib therapy and cytotoxic DTX therapy; the antitumor efficacy of combination therapy was well-validated by ex vivo Ki-67 staining, and posttreatment imaging further confirmed that after combination therapy, the tumor signatures of glucose metabolic activity, integrin $\alpha_v$$\beta_3$ expression, and VEGF levels were all significantly reduced.

All the imaging agents used in this study, besides BLI, could be easily modified for clinical use. The NIRF probe could be adapted for PET and SPECT, and multiplexed imaging could then be performed in the same patient by carefully designing the imaging procedures. Alternatively, optical imaging could also be used for intraoperative imaging-guided tumor surgery. Taken together, the results of this study suggest that the combination of multiparameter imaging could provide a better understanding of simultaneous tumor signatures. A complete overview of all available tumor signatures would facilitate improved guidance for cancer therapy and may eventually lead to personalized cancer therapy being feasible.

CONCLUSION

We demonstrated the feasibility of using multiple molecular imaging approaches for target-specific and functional identification of multiple tumor signatures in vivo, which allowed the rational design of dasatinib combination tumor therapy. This approach could noninvasively determine tumor responses associated with cancer therapeutic interventions and may facilitate accelerating the development of new cancer therapies.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This work was supported, in part, by “973” projects (2013CB733802 and 2011CB707705), National Natural Science Foundation of China (NSFC) projects (81471712, 81222019, 81125011, and 81371614), grants from Beijing Natural Science Foundation (7132131 and 7132123), and a grant from the Beijing Nova Program (Z121107002512010). No other potential conflict of interest relevant to this article was reported.

REFERENCES

25. Klinghoffer RA, Sachsenmaier C, Cooper JA, Soriano P. Src family kinases are function as $\alpha_v$$\beta_3$ function as a predictor of the antimigratory and antiproliferative effects of dasatinib. Cancer Res. 2009;69:3173–3179.
34. Klinghoffer RA, Sachsenmaier C, Cooper JA, Soriano P. Src family kinases are function as $\alpha_v$$\beta_3$ function as a predictor of the antimigratory and antiproliferative effects of dasatinib. Cancer Res. 2009;69:3173–3179.
Molecular Imaging of Post-Src Inhibition Tumor Signatures for Guiding Dasatinib Combination Therapy

Liquan Gao, Hao Liu, Xianlei Sun, Duo Gao, Chenran Zhang, Bing Jia, Zhaohui Zhu, Fan Wang and Zhaofei Liu

Published online: September 17, 2015.
Doi: 10.2967/jnumed.115.158881

This article and updated information are available at:
http://jnm.snmjournals.org/content/57/2/321

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml