An In vivo Model of Met-Driven Lymphoma as a Tool to Explore the Therapeutic Potential of Met Inhibitors

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Abstract Purpose: Met, the tyrosine kinase receptor for hepatocyte growth factor, is frequently deregulated in human cancer. Recent evidence indicates that Met amplification may confer resistance to treatments directed toward other receptor tyrosine kinases. Thus, there is a need to develop Met inhibitors into therapeutic tools, to be used alone or in combination with other molecularly targeted drugs. Preclinical validation of Met inhibitors has thus far been done in nude mice bearing cancer cells xenografts. A far superior model would be a transgenic line developing spontaneous Met-driven tumors with high penetrance and short latency.

Experimental Design: To this end, we introduced into the mouse genome TPR-MET, the oncogenic form of MET. The Tpr-Met protein ensures deregulation of Met signaling because dimerization motifs in the Tpr moiety independently activate the Met kinase.

Results: Here, we describe a TPR-MET transgenic line that develops thymic T-cell lymphoma with full penetrance and very short latency. In the tumors, Tpr-Met and its effectors were phosphorylated. Treatment of tumor-derived T lymphocytes with the selective Met inhibitor PHA-665752 at nanomolar concentrations abolished phosphorylation of Met and downstream effectors and led to caspase-mediated apoptosis. I.v. administration of PHA-665752 to transgenic mice bearing lymphomas in exponential growth phase led to a significant decrease in tumor growth and, in some cases, to tumor regression.

Conclusions: Our transgenic line, which within 2 months reliably develops Tpr-Met–driven T-cell lymphoma, represents a valuable tool to explore the efficacy and therapeutic potential of Met kinase inhibitors as anticancer drugs.

Targeted approaches are expected to revolutionize cancer treatment in the near future (1). Receptor tyrosine kinases are among the most actively pursued targets (2). To date, a number of small molecule inhibitors (generally ATP analogues) are already either approved (3) or undergoing clinical trials (2). Although treatment with specific inhibitors may result in resistance due to mutations in the target (4) or to amplification of other receptor genes (5), this can be bypassed by using them in combination or together with other molecular tools.

Met is the tyrosine kinase receptor for hepatocyte growth factor (HGF)/scatter factor. This ligand/receptor pair is involved in cell survival, proliferation, and migration (6). Deregulated Met activation has been linked to cancer predisposition and metastasis (6–8), and frequently correlates with poor prognosis in carcinomas, sarcomas, and hematological cancers (7). The potential involvement in such a vast array of cancers has stimulated the search for Met inhibitors (9). Recent results suggest that subsets of patients with gastric (10) or lung cancers (5) with Met amplification may be appropriate for clinical trials with Met inhibitors. Thus, there is a need of animal models for preclinical testing of such compounds. Thus far, this has been done in nude mice transplanted with tumor cells overexpressing Met, such as GTL-16 cells (11). However, nude mice have profound defects in their immune response and tend to be exceedingly sensitive to novel treatments. Furthermore, the composition of transplanted tumors is homogeneous, whereas spontaneous tumors are a mix of different cells. Lastly, xenografts fail to recapitulate tumor-host stromal interactions (12). Transgenic models of tumorigenesis obtained by expressing the dominant oncogene of interest in a tumor-prone...
background would be preferable (12). However, ideally, the tumors should be highly penetrant, latency should be short, and the model should require simple breeding schemes and a minimum of genotyping (12).

Several models of HGF/Met-dependent tumorigenesis have been described. Transgenic mice with inducible expression of human Met in hepatocytes developed hepatocellular carcinoma with 85% penetrance but with a long latency (10 months; ref 13). Knock-in mice with mutations in the met locus developed various tumors, with an incidence ranging from 44% to 89% depending on the mutation. These mice, however, had a life span of up to 2 years, and the tumors were often discovered only at necropsy (14). Transgenics ectopically expressing the Met ligand HGF/ scatter factor developed a variety of tumors, among which rhabdomyosarcoma and melanoma, with latencies of over a year (15–17). To accelerate the appearance of both types of tumors, it was necessary to move the transgene in the Ink4-/- background (16) and to use UV treatment for the melanomas (18). In an early work, Liang et al. (19) described a transgenic line obtained with TPR-MET, the rearranged oncogenic form of the receptor (20). In these mice, TPR-MET expression was driven by the murine metallothionein promoter. When kept in continuous breeding for at least 6 months, they developed mainly mammary tumors. Altogether, these models, although useful to understand the role of HGF/Met in tumorigenesis, do not fulfill the optimal requirements for preclinical use mentioned above.

In this work, we describe a T-cell lymphoma that arises with 100% penetrance and very short latency (2 months) in transgenics expressing the oncogenic form of Met, Tpr-Met, in thymocytes. In Tpr-Met, dimerization of the Tpr moiety promotes constitutive activation of the kinase domain of the human Met receptor (21). The model is based on a single transgene; thus, breeding and genotyping are reduced to a minimum. The course of the disease is very rapid but the tumors can be diagnosed before the appearance of symptoms by magnetic resonance imaging (MRI). We show that treatment of tumor-derived T lymphocytes with nanomolar concentrations of a powerful and specific Met inhibitor (PHA-665752) leads to inactivation of the Met kinase and its effectors, and to their death due to apoptosis. We also show that administration of the same drug to the TPR-MET transgenics results in reduction of tumor growth. We propose the TPR-MET transgenic mouse as the model of choice for preclinical studies of Met inhibitors.

**Materials and Methods**

Reagents and antibodies. All reagents, unless specified, were from Sigma-Aldrich. PHA-665752 (3Z)-5-[(2,6-dichlorobenzyl)sulfonyl]-3-[(3,5-dimethyl-4-1H-pyrrol-2-yl)methylene]-1,3-dihydro-2H-indol-2-one (Pfizer, Inc.) was suspended in DMSO and kept in small aliquots at

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**Fig. 1.** Characterization of TPR-MET transgenic (Tg) mice. A, the Tpr-Met-TRE-GFP responder construct used to generate the transgenic line, kb, kilobases. B, autopsies of TPR-MET transgenic mice showing a massively enlarged thymus. C, H&E stain showing histology of TPR-MET transgenic lymphoma (>200). D and E, green fluorescent protein visualization by fluorescence of the tumor and tumor-derived thymocytes. F, representative Western blot with anti-Met antibodies of protein extracts (30 µg) of different tissues from a tumor-bearing TPR-MET transgenic mouse. G, survival curves of the Tpr-Met transgenic and controls lines. H, MRI of thymus (red arrows) in the TPR-MET transgenic line at different stages of tumor development. Left, pretumoral stage; middle, lymphoma at an early stage of development; right, lymphoma at an advanced stage of development.
into the pBl-eGFP vector (Clontech) under control of the TetO2-responsive element fused to the bidirectional cytomegalovirus minimal promoter to generate the Tpr-Met-TRE-GFP responder construct (Fig. 1A). The Tpr-Met-TRE-GFP construct was microinjected into the fertilized eggs of FVB mice in the San Raffaele-Telethon Core Facility for Conditional Mutagenesis. Founder mice were identified by PCR analysis of genomic DNA prepared from tail biopsies. Founder of line 8 died at 3.5 mo due to a thymic lymphoma. In this line, transmission of the transgene followed a typical Mendelian inheritance pattern, and all the transgenic progeny established from this founder died between ages 2 and 3 mo with the same pathology. Nontransgenic littermates exhibited no sign of the disease. The line was maintained in the heterozygous state in the FVB background. Mice were genotyped by PCR analysis of tail genomic DNA. The primers for Tpr-Met-TRE-GFP transgene were 5′-AGA GGA GCC CCT CCT TAT CC-3′ and 5′-GGT CCC CAA ACT CAC CCT GAA GTT CTC-3′. PCR amplification yielded a 665-bp fragment. In vivo imaging of green fluorescent tumors was done with a LT-9500-220 Illumatool tunable lighting system (Lihtools Research) and imaged by an Olympus Camedia camera. All animal procedures were approved by the Ethical Commission of the University of Torino, Italy, and by the Italian Ministry of Health. Survival curves were done by using the nonparametric model of Kaplan-Meyer.

Western blot analysis. Cells were washed with ice-cold PBS and lysed in lysis buffer [20 mmol/L Tris (pH 7.5), 150 mmol/L NaCl, 1 mmol/L EDTA, 1 mmol/L EGTA, 1% Triton X-100, and 1 mmol/L glyceraldehyde-3-phosphate] with protease inhibitor cocktail, 1 mmol/L sodium-orthovanadate, and 1 mmol/L phenylmethylsulfonyl fluoride. Protein lysates were cleared of cellular debris by centrifugation at 4°C for 10 min at 12,000 × g, quantified using Bio-Rad protein assay, resolved in 7.5% or 10% SDS-PAGE gels, and transferred to Hybond-C Extra nitrocellulose membranes (Amersham Biosciences). Proteins were visualized with horseradish peroxidase–conjugated secondary antibodies and Super Signal West Pico Chemiluminescent Substrate (Roter). Western blot results were confirmed in at least three independent experiments.

Cell proliferation assay and cell cycle analysis. Cell proliferation was evaluated by Trypan-blue exclusion. Briefly, 1 × 10⁵ cells per well were seeded in a 24-well plate and increasing concentrations of PHA-665752, or an equal volume of diluent (DMSO) were added to complete medium. Cell number was evaluated after 24 h of treatment. Proliferation was expressed in percentage relative to day 0. Each experiment was repeated thrice independently. Experimental data are presented as mean ± SD. For the cell cycle analysis, triplicate Tpr-Met T-cell lymphocyte cultures were grown in RPMI with 10% fetal bovine serum and treated with a final concentration of 60 to 250 nmol/L of PHA-665752 or an equal amount of diluent (DMSO) as a control for 8 h. Cells were then collected, stained with propidium iodide, and analyzed with a Becton Dickinson FACScan and CellQuest software.

Histology and immunohistochemistry. For the histologic and immunohistochemical analyses, tissue samples were fixed in PBS-buffered formalin (10%) and subsequently embedded in paraffin. De waxed 4-μm–thick tissue sections were stained with H&E or processed with four antigen retrieval cycles of 5 min each in microwave oven (800 W) in citrate buffer pH 6. After blocking for 1 h at room temperature with 0.1% Triton X-100 and 10% normal goat serum in PBS, the sections were incubated with primary antibodies in the same solution at room temperature overnight. Primary antibodies were added at a dilution of 1:300. Sections were further processed with biotinylated secondary antibodies (1:300) and the avidin-biotin-peroxidase complex (Vector) and finally visualized with 3,3'-diaminobenzidine (Roche).

MRI detection of T-cell lymphomas and volume determination. Magnetic resonance images were acquired on a Bruker Avance 300 spectrometer (7 T) equipped with a Micro 2.5 microimaging probe and animal handling unit. Multislice rapid acquisition with relaxation enhancement (RARE) images were acquired using the following settings: repetition time, 10.0 s; effective echo time, 79.3 ms; RARE factor, 128; n = 2 repetitions; 128 × 128 matrix; slice thickness, 1 mm; and field of view, 40 × 40 mm; resolution, 312.5 μm. Tumor volumes were

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**Fig. 2.** Biochemical characterization of T lymphocytes extracted from fresh tumor samples of TPR-MET transgenic mouse and non-transgenic littermates. Representative Western blot of transgenic and control thymocytes. Thirty micrograms of protein extracts (see Materials and Methods) were loaded in each lane. Antibodies against the indicated phosphorylated effectors were used to detect their activated forms. Tubulin represents a loading control.

**Cell lines and cell culture.** Primary Tpr-Met T-cell lymphocytes were obtained from fresh thymic tumors. Human anaplastic large lymphoma cells were kindly provided by Prof. G. Inghirami, Center for Experimental Research and Medical Studies, University of Torino, Torino, Italy. Tpr-Met T-cell lymphocyte lines were obtained from fresh thymic tumors after being cultured for several passages in complete RPMI 1640. All cell lines were cultured in RPMI 1640 supplemented with 10% fetal bovine serum at 37°C in an atmosphere. The experiments involving the use of cell lines were always repeated at least three times independently. Experimental data are presented as mean ± SD. For the cell cycle analysis, triplicate Tpr-Met T-cell lymphocyte cultures were grown in RPMI with 10% fetal bovine serum and treated with a final concentration of 60 to 250 nmol/L of PHA-665752 or an equal amount of diluent (DMSO) as a control for 8 h. Cells were then collected, stained with propidium iodide, and analyzed with a Becton Dickinson FACScan and CellQuest software.

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Fig. 3. Effects of PHA-665752 on tumor-derived TPR-MET T-cell lymphocytes. A, B, PHA-665752 inhibits proliferation and induces cell death in tumor-derived T cells of TPR-MET transgenic mice but not in tumor-derived T cells of NPM-ALK transgenics. C, representative Western blot showing suppression of MET-dependent phosphorylations by PHA-665752 in a tumor-derived TPR-MET T-cell lymphocyte cell line. D, fluorescence-activated cell sorting analysis of propidium iodide-stained cells after 8 h of treatment with 60 to 250 nmol/L PHA-665752, showing an increase in the sub G₀-G₁ population (16-63%). E, Western blot of cleaved caspase 3, 6, 7, and 9 indicating induction of apoptosis in Tpr-Met lymphoma cells after treatment with PHA-665752 (250 nmol/L for 5-8 h).
calculated by drawing regions of interest around the tumor on every slice, adding them together, and multiplying for the slice thickness.

In vivo studies. Daily treatment with PHA-665752 given i.v. were initiated when tumors were 200 to 300 mm³ in volume. Tumor volume was expressed in percentage relative to day 1 as the median FSD indicated for groups of mice. Percent (%) inhibition values were measured on the final day of study for drug-treated compared with vehicle-treated mice and are calculated as 1 - [(TreatedFinal day - TreatedDay 1)/(ControlFinal day - ControlDay 1)]. Significant differences between the treated versus the control groups were determined using nonparametric Mann-Whitney test.

Results

Description of the model. Our original aim was to generate a Tet-inducible model of Tpr-Met–mediated tumorigenesis. The TPR-MET cDNA was thus subcloned in the bidirectional responder plasmid pBI-eGFP (Clontech), which, upon transactivation, coexpresses the eGFP reporter with the transgene of interest (Fig. 1A). After microinjection in fertilized eggs, several independent transgenic lines were obtained. In line 8, transmission of the transgene followed a typical Mendelian mode, indicating integration of the construct in a single site. Unexpectedly, all transgenics of this line (but none of the nontransgenic lintermates) died starting at 2 months of age with signs of respiratory insufficiency. Necropsy revealed a massively enlarged thymus (Fig. 1B). Histologic analysis confirmed the presence of a thymic lymphoma (Fig. 1C). Flow cytometry of the cells derived from the tumors indicated a population of thymic origin (Thy-1⁺, B220⁺, CD19⁺, CD11b⁻, and NK⁻) at an intermediate stage of maturation, corresponding to a double-positive stage of thymocyte differentiation (CD4⁺ and CD8⁻⁻).

The tumors (Fig. 1D and F) and the lymphocytes isolated from them (Fig. 1E and Fig. 2) were always positive for both eGFP and Tpr-Met, whereas expression of the transgenes was found only occasionally in the spleen (Fig. 1F) and lymphnodes, and never in any other tissue. The fact that the transgenes were expressed in the absence of a transactivator, the tissue specificity of expression and the results of inverse PCR (to be published elsewhere) indicate that integration of the responder construct occurred in a chromatin region actively transcribed in thymocytes. The absolute correlation between Tpr-Met expression and the development of lymphoma suggests that the tumors were Tpr-Met dependent.

Kaplan-Meyer analysis of the animals’ lifespans showed in the transgensics a mean survival of 87 days and complete penetrance of the malignancy (cumulative incidence of 100%; Fig. 1G). Nontransgenic siblings did not develop thymic lymphoma or any other tumor. The transgenic animals generally died within 10 days from the first signs of respiratory insufficiency (on the average, age 2.5 months). Autopsy at the appearance of symptoms revealed that the tumors were already at an advanced stage (Fig. 1B). However, the lymphoma could be diagnosed...
when the mice were still asymptomatic by using MRI (Fig. 1H, middle). This analysis (n = 20; data not shown) allowed us to establish that the mean latency was of the order of 2 months.

Biochemical analysis of Tpr-Met–driven thymic lymphoma. Activation of the Met receptor by HGF induces phosphorylation of downstream effectors (7). We verified phosphorylation of some of these in lymphocytes extracted from fresh tumor samples, using as control thymocytes extracted from non-transgenic littermates (Fig. 2). Tumor lymphocytes expressed Tpr-Met. Phosphorylation of both the activation loop tyrosines (p-Tyr 1230/34/35) and the major docking site tyrosine (p-Tyr 1356; ref. 23) confirmed activation of the Met kinase. STAT5 and AKT were preferentially activated (phosphorylated on Tyr694 and on Ser473, respectively) in tumor lymphocytes compared with control cells. Conversely, STAT3 and FAK phosphorylation was comparable in tumor and in control lymphocytes. Extracellular signal-regulated kinase 1/2, which is a well-known Met effector, had a very low phosphorylation level in both tumor and control cells. Similar patterns of overall effector phosphorylation were found in several stable cell lines established from the Tpr-Met lymphomas. These results confirmed that in the tumors of our transgenic model, the major signaling pathways downstream of Met were constitutively activated.

Effect of PHA-665752 on proliferation/apoptosis of the Tpr-Met T-cell lymphocytes. We next treated tumor-derived cell lines with PHA-665752, a selective and powerful Met inhibitor (IC_{50} of 9 nmol/L; ref. 11). Cells were treated with a single dose of PHA-665752 and were counted 24 hours later. In Tpr-Met T lymphocytes, increasing concentrations of the drug caused a decrease in proliferation. Beginning at 60 nmol/L PHA-665752, there was a dramatic reduction in cell number, indicating cell death (Fig. 3A). As a control, we treated with PHA-665752 T cells established from NPM-ALK–driven lymphomas (24). Proliferation of these cells was unaffected by PHA-665752 at concentrations up to 1 μmol/L (Fig. 3B). Thus, the effect of the Met-directed drug was specific for T lymphocytes from the tumors of Tpr-Met transgenic mice.

To verify the effect of PHA-665752 on Met signaling, tumor-derived T-cell lines were treated with increasing concentrations of PHA-665752 for 2 hours. The phosphorylation of Tpr-Met and of some downstream effectors was analyzed by Western blot (Fig. 3C). Phosphorylation of Tpr-Met at both the activation loop tyrosines (p-Tyr 1230/34/35) and the COOH-terminal tail major docking site (p-Tyr 1356) was completely abolished at concentrations higher than 60 nmol/L. PHA-665752 also inhibited in a dose-dependent manner phosphorylation of STAT5, AKT, FAK, and extracellular signal-regulated kinase 1/2. Phosphorylation of the latter, almost undetectable in lymphocytes freshly extracted from the tumors (Fig. 2), was relatively higher in the stable T-cell lines and was abolished by the Met inhibitor (Fig. 3C). Conversely, the basal phosphorylation of STAT3 was not affected by PHA-665752 treatment up to 1 μmol/L (data not shown), indicating that in these cells, phosphorylation of this effector is probably sustained by other growth factors.

We next verified the effects of inhibition of Tpr-Met signaling on the cell cycle. Tpr-Met T-lymphocyte cell lines were treated with vehicle or increasing concentrations of PHA-665752 for 8 hours, and their distribution in the cell cycle was analyzed by propidium iodide staining and fluorescence-activated cell sorting. PHA-665752 (250 nmol/L) caused a dramatic increase in cell death (from 12-63%) in Tpr-Met T cells (Fig. 3D; M4). To confirm this observation, we assayed caspase 3, 6, 7, and 9 activation. Western blot analysis showed that all these caspases were activated, beginning at 5 hours of treatment with 250 nmol/L PHA-665752 (Fig. 3E).

PHA-665752 treatment in vivo shows antitumor efficacy in the Met-driven lymphoma model. Altogether, the results described above imply that the T-cell lymphomas arising in transgenic line 8 were Tpr-Met-driven. Thus, we considered the model appropriate to test the efficacy of PHA-665752 in vivo.

To obtain a homogenous cohort of animals, the presence of lymphoma and its volume were determined in transgenic animals by MRI scanning. A volume cutoff for treatment was established at 200 mm^3. Mice with tumors (200 to 300 mm^3) were randomly divided into two groups (n = 7). PHA-665752 (25 mg/kg; ref. 11) was injected i.v. daily for 7 days. Control animals were treated with vehicle alone. Tumor growth was monitored by MRI scanning twice (at day 4 and 7) during the treatment. Due to variability in tumor volume at the start of the treatment, data were normalized and expressed in percentage relative to day 1. At the end of the treatment, PHA-665752 reduced tumor growth by 82% with respect to vehicle-treated controls (P < 0.003; Fig. 4A). A reduction in tumor growth occurred in all treated mice. Two of seven of the treated animals exhibited a shrinkage in tumor volume. To evaluate whether the effect of PHA-665752 was associated with inhibition of Met signaling, we compared tumor lymphocytes from mice treated for 2 hours with vehicle or with a single dose of PHA-665752. Acute treatment with the drug resulted in a marked reduction in the phosphorylation levels of Tpr-Met, STAT5, and AKT (Fig. 4B). We also evaluated by Ki67 and cleaved caspase 3 staining the presence of proliferating versus apoptotic cells in tumor sections of treated and untreated animals. Tumor growth was compared for the presence of Ki67 staining and cleaved caspase 3. A decrease in proliferation and an increase in cell death (from 12-63%) in Tpr-Met T cells (Fig. 3D; M4). To confirm this observation, we assayed caspase 3, 6, 7, and 9 activation. Western blot analysis showed that all these caspases were activated, beginning at 5 hours of treatment with 250 nmol/L PHA-665752 (Fig. 3E).

Discussion

In this work, we described a T-cell lymphoma that arises with short latency and full penetrance in TPR-MET transgenics. The model resulted from the insertion of the TPR-MET cDNA in a genomic region that harbors a series of genes selectively expressed in thymocytes. Although a vast body of literature is available on the role of Met in B-cell development and related malignancies (25), less is known on its role in T cells. Met has been described as a mediator of T-cell differentiation (26). In the TPR-MET transgenics, constitutive Met activation stopped thymocytes development by freezing them at an immature state. Among the signaling molecules activated in the tumors, STAT5, previously shown to be a Met effector in long term cultures of human hepatocytes was particularly prominent (27). Interestingly, transgenic mice expressing STAT5 proteins in the lymphoid compartment develop in time thymic CD8+ T-lymphoblastic lymphomas (28). Thus, it is likely that in our model, Tpr-Met–dependent sustained STAT5 activation contributes to the development of
the T-cell malignancy. In humans, it has been shown that Met is expressed in adult T-cell leukemia in the acute stage, and that HGF induces proliferation of a Met-positive adult T-cell leukemia cell line (29). Thus, the HGF-Met axis could be a potential therapeutic target for adult T-cell leukemia.

In this work, we first assessed the effects of a powerful and specific Met inhibitor (PHA-665752) on the viability of the malignant T cells derived from the Tpr-Met transgenics. Treatment with PHA-665752 caused inactivation of the Met kinase and induced cell death beginning at 60 nmol/L, indicating high sensitivity to the drug. This result on one side confirmed the dependency of the malignancy on Tpr-Met expression and, on the other, suggested that the drug could be effective also in vivo.

To test the effect of PHA-665752 in vivo, it was necessary to diagnose the tumor before the appearance of clinical signs because, thereafter, the course of the disease is very rapid. We showed that it is possible to detect the lymphoma and to stage it by size through MRI. In our conditions (beginning treatment at 200 to 300 mm³), daily PHA-665752 administration for 1 week had a dramatic inhibitory effect on tumor growth. However, reduction of tumor volume occurred only in two cases. Because in vitro PHA-665752 treatment resulted in T-cell death within 24 hours, in vivo Tpr-Met-driven T-lymphoma cells might be protected by stromal growth factors. More likely, the activity of the inhibitor in vivo may be limited by local biological barriers, such as the basal membrane, or by the intrinsic chemical properties of the compound (e.g., solubility and half life).

Biochemical analysis of malignant lymphocytes recovered from the tumors 2 hours after injection of the drug indicated inhibition of phosphorylation of Tpr-Met and of its effectors. Slices of tumor samples recovered 12 hour after injection of the drug showed a clear reduction in the number of proliferating cells and an increase in cells undergoing programmed cell death. Although our results confirmed that PHA-665752 is a good lead compound, the in vivo model also revealed that it is not appropriate to use as a drug as such. In fact, upon injection, the compound has a tendency to precipitate in the lung. Prolonged treatment with PHA-665752 is impossible due to the scarce solubility of the drug in aqueous solution. Recently, another Pfizer Met inhibitor has been described, with better pharmacokinetics, higher tolerability, and formulated to be administered p.o. (30). Although the latter seems to be less selective, its potency seems to be comparable with that of PHA-665752. The results described above show that the transgenic model of Tpr-Met-driven lymphoma could be appropriate to test in vivo the efficacy of this and of any other Met inhibitor previously validated in cultured cells.

Validating novel inhibitor(s) in the spontaneous murine lymphoid tumor that we developed could contribute to speed up approval of phase I clinical trials on patients with adult T-cell leukemia (29), as well as on cases of Met-amplified gastric cancers (10) or Gefitinib-resistant non–small cell carcinoma of the lung (5).

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References

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