Development of STI571 and Its Use in Chronic Myelogenous Leukemia and Other Malignancies

By Michael J. Mauro, MD, Michael E. O'Dwyer, MD, and Brian J. Druker, MD

ABSTRACT

Chronic myelogenous leukemia (CML) is a clonal hematopoetic stem cell disorder characterized by the (9:22) translocation and resultant production of the constitutively activated Bcr-Abl tyrosine kinase. Characterized clinically by marked myeloid proliferation, it terminates invariably in an acute leukemia. Conventional therapeutic options include interferon-based regimens and stem cell transplantation, with stem cell transplantation being the only curative therapy. Through rational drug development, STI571, a Bcr-Abl tyrosine kinase inhibitor, has emerged as a paradigm for gene product targeted therapy, offering new hope for expanded treatment options for patients with CML.

Oncology Spectrums *2001;2(8):536-541*

INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder that results from the clonal expansion of a transformed hematopoetic stem cell. Following an initial chronic phase lasting a median of 4–5 years, CML progresses to an accelerated phase of variable duration that heralds transition to a terminal acute leukemia (blast crisis). Current treatment choices for CML include stem cell transplantation, hydroxyurea, or interferon-alpha (IFN-α)–based regimens, with allogeneic stem cell transplantation being the only proven curative therapy for CML.[1] However, the average age of onset of CML is greater than 50 years of age; this factor, combined with the inability to identify a suitably matched donor in every case, limits this option to a minority of patients. Thus, less than 20% of CML patients are cured with current treatment options.[2,3] Against this background, it is clear that there is a need for better therapies for CML.

An understanding of the molecular pathogenesis of CML has fostered the development of a specific, molecularly targeted therapy for CML. This article focuses on the identification and characterization of the causative genetic abnormality in CML and the development and success of a gene product targeted therapeutic agent, STI571. The potential for using STI571 in other malignancies will also be discussed.

CML AND BCR-ABL

The unraveling of the molecular pathogenesis of CML began in 1960, when Nowell and Hungerford described the presence of a consistent chromosomal abnormality in CML patients.[4] This was the first example of a malignancy linked to a consistent chromosomal abnormality. It later became apparent that the abnormality described by Nowell and Hungerford was a shortened chromosome 22. Rowley later showed that the shortened chromosome, the so-called Philadelphia chromosome, was not the result of a chromosomal deletion but was the product of a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9:22)(q34;q11).[5] The molecular consequence of this event is the generation of a chimeric *bcr-abl* gene, formed by juxtaposition of the *c-abl* oncogene on chromosome 9 with sequences from the breakpoint cluster region (*bcr*) on chromosome 22.[6–8]

Depending on the breakpoint in *bcr*, various chimeric fusion proteins can result: p210 (210kDa), p185 (a 185kDa protein), and, rarely, p230 (Figure 1). The protein p210

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

Through rational drug development, STI571, a Bcr-Abl tyrosine kinase inhibitor, has emerged as a paradigm for gene product targeted therapy, offering expanded treatment options for patients with chronic myelogenous leukemia.

Drug levels predicted to be effected from preclinical studies corresponded to clinically effective doses, and the clinical trials with STI571 indicate that endpoints besides maximally tolerated dose need to be incorporated into early clinical trials with molecularly targeted agents.

The side-effect profile of STI571 is minimal as compared to standard treatments for leukemia, and this oral agent can be administered as outpatient therapy.

The profile of inhibition of kinases for STI571 suggests that it should have activity in other diseases such as gastrointestinal stromal tumors.

Dr. Mauro and Dr. O'Dwyer are assistant professors of medicine at the Leukemia Center at the Oregon Cancer Institute of Oregon Health Sciences University in Portland, where Dr. Druker is director.

Acknowledgements: Dr. Druker's research has been funded by grants from the National Cancer Institute, a Translational Research Award from the Leukemia and Lymphoma Society, and a Clinical Scientist Award from the Burroughs Wellcome Fund.

Bcr-Abl results from fusion of the c-abl proto-oncogene at exon 2 with *bcr* sequences at either exon 13 or 14 (formerly b2 and b3 [Figure 1]). In either case, this generates a 210kDa protein seen in 95% of patients with CML. Fifteen to 30% of adults with acute lymphoblastic leukemia (ALL) are Philadelphia chromosome positive [Ph(+)]; half of these patients bear the p210 fusion, the other half the p185 product. The p185 (also called p190) Bcr-Abl results from fusion of the same sequences of *c-abl* with a proximal site in *bcr* (exon 1). Additionally, 5% of childhood ALL patients are Ph(+), with 80% of these patients bearing the p185 Bcr-Abl product. The p230 fusion results from fusion of *c-abl* sequences at a downstream site in *bcr*. This rare event is associated with the chronic neutrophilic variant of CML.

TRANSFORMING ABILITY OF BCR-ABL

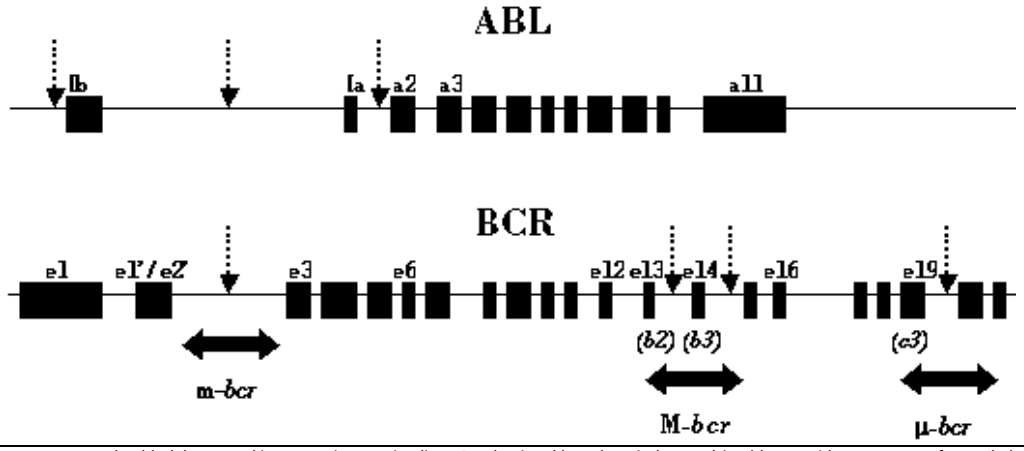
Additional insight into the pathogenesis of CML came from the study of transforming retroviruses, specifically the Abelson murine leukemia virus.[10] The transforming gene of this virus, *v-Abl* was shown to be a tyrosine kinase with its transforming ability dependent on this tyrosine kinase activity.[11,12] Subsequently, the Bcr-Abl fusion product proved to display similar tyrosine kinase activity essential for leukemic transformation.[13] Unlike the normal c-Abl gene product, which is nuclear and cytoplasmic in location and have tightly regulated kinase activity, the Bcr-Abl fusion proteins are exclusively localized to the cytoplasm and have constitutively increased tyrosine kinase activity. The Bcr-Abl fusion gene product transforms fibroblasts and hematopoetic progenitors in bone marrow culture, and it renders myeloid cell lines cytokine independent.[13-15] Moreover, transduction of p210 *bcr-abl* into murine hematopoetic stem cells followed by transplantation into syngeneic mice causes a CML-like syndrome,[16,17] and mice transgenic for p190 *bcr-abl* develop acute leukemia.[18] These findings provide the most convincing evidence that *bcr-abl* is a leukemic oncogene and is the causative molecular abnormality in CML and in Ph(+) ALL.

The mechanism whereby Bcr-Abl tyrosine kinase activity leads to the phenotypic abnormalities seen in CML is not entirely clear, but it has been studied intensively over the past decade. The constitutive tyrosine kinase activity of Bcr-Abl causes activation of a variety of intracellular signaling pathways leading to alterations in the proliferative, adhesive, and survival properties of CML cells.[19] However, all of these events are dependent on the tyrosine kinase activity of the Bcr-Abl protein.

STI571 AND THE DEVELOPMENT OF TARGETED THERAPY

As the tyrosine kinase activity of the Bcr-Abl proteins is essential for their transforming abilities, it was predicted that a specific inhibitor of the Abl protein tyrosine kinase would be an effective therapeutic agent for CML and other *bcr-abl*–positive leukemias (Figure 2). Given the high degree of homology between different kinase domains, there was initial skepticism that specific tyrosine kinase inhibitors could be developed. However, Yaish et al,[20] in 1988 reported the synthesis of a class of compounds known as the tyrphostins, which displayed specificity for individual tyrosine kinases; one of this class of compounds was subsequently shown to be capable of inhibiting the Bcr-Abl kinase and of killing Bcr-Abl–expressing cells in vitro (Anafi).[21] In parallel, scientists at Ciba-Geigy

FIGURE 1. SCHEMATIC REPRESENTATION OF THE *abl* AND *bcr* GENES INVOLVED IN T(9:22)(Q34;Q11).



Exons are represented as black boxes and introns as intervening lines. Breakpoints (dotted vertical arrows) in *abl* occur either upstream of exon Ib, between Ib and Ia, or between Ia and a2. Breakpoints in *bcr* usually occur in one of three breakpoint cluster regions (*bcr*; horizontal gray arrows); those in m-*bcr* leading to mRNA with an e1a2 junction (p185 protein); those in M-*bcr* (p210 protein) occurring between exon 13 and 14 (formerly b2 and b3) or between exons 14 and 15 (b3 and b4); and those in -*bcr* at exon 19 (e19a2) resulting in the p230 protein.

Adapted with permission from *Curr Oncol Rep.* © 2000 Current Sci (US).
Mauro MJ, O'Dwyer ME, Druker BJ. *Oncology Spectrums.* Vol 2. No 8. 2001.

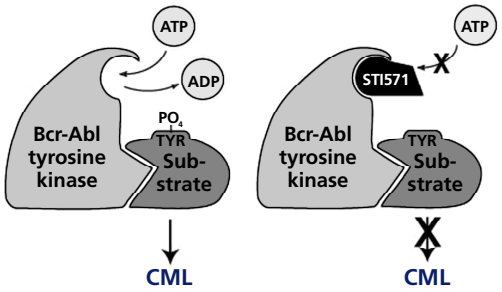
Pharmaceuticals (now Novartis) identified a lead kinase inhibitor by screening a large library of compounds against specific kinases. A series of compounds related to the lead inhibitor were synthesized and screened for their abilities to inhibit a panel of protein kinases; among these, STI571 (formerly CGP57148B and now imatinib mesylate or Gleevec) was found to be a potent and selective inhibitor of the *abl* protein tyrosine kinase. Aside from its effects on the *abl* kinases, the only other kinases inhibited by STI571 are the platelet-derived growth factor receptor (PDGFR) tyrosine kinase (the original target for the compound) and *c-kit*.

PRECLINICAL STUDIES OF STI571

Studies in our laboratory showed that STI571 specifically inhibited proliferation of myeloid cells containing the Bcr-Abl fusion protein.[22] Additionally, in colony-forming assays of peripheral blood or bone marrow from patients with CML that was incubated with 1 µM STI571, there was a 92–98% decrease in the number of *bcr-abl*-(+) colonies formed, but minimal inhibition of normal colony formation. Similarly, Deininger et al[19] and Marley et al[23] showed maximal inhibition of colony formation in CML-patient samples with 1 µM STI571 (Deininger).[24] Selective effects of STI571 on CML progenitors vs normal progenitors has also been demonstrated in long-term marrow culture studies.[25]

Using cell lines, dose-dependent inhibition of proliferation and subsequent induction of apoptosis were observed in six lines derived from Bcr-Abl-(+) leukemias after exposure to STI571; similar effects were observed in 12 consecutive CML-patient samples as well as two Ph(+) ALL samples.[26] Exposure to STI571 also inhibits proliferation of p185 expressing ALL-derived cell lines as well as p185 Bcr-Abl(+) leukemic blasts.[27,28] In all of these in vitro studies, concentrations of 1 µM or less of STI571 proved to be maximally effective. Also, animal studies have shown that STI571 produces a dose-dependent inhibition of Bcr-Abl-(+) tumor formation.[22] With dosing providing continuous exposure, STI571 was able to eradicate Bcr-Abl-(+) tumors in nude mice.[29] Prior to clinical testing, STI571 was shown to have an acceptable animal toxicology profile.

FIGURE 2. SCHEMATIC REPRESENTATION OF THE MECHANISM OF ACTION OF STI571



The Bcr-Abl tyrosine kinase is a constitutively active kinase that functions by binding ATP and transferring phosphate from ATP to tyrosine residues on various substrates. This activity causes the excess proliferation of myeloid cells characteristic of CML. STI571 functions by blocking the binding of ATP to the Bcr-Abl tyrosine kinase, thus inhibiting the activity of the kinase. In the absence of tyrosine kinase activity, substrates required for Bcr-Abl function cannot be phosphorylated.

Mauro MJ, O'Dwyer ME, Druker BJ. *Oncology Spectrums.* Vol 2. No 8. 2001.

CLINICAL STUDIES

A Phase I clinical trial with STI571 started in June, 1998. This trial was a dose escalation study, designed to establish the maximum tolerated dose (MTD) with a secondary endpoint of clinical efficacy. Patients were eligible if they were in the chronic phase of CML and had failed therapy with IFN-α. STI571 was administered as once daily oral therapy and no other cytoreductive agents were given. Once doses of 300 mg or greater were reached, 53 of 54 patients achieved a complete hematologic response.[30] Responses were typically seen within the first 3 weeks of therapy and have been maintained in 51 of 53 patients, with a median duration of follow-up of 310 days. At this dose level (300mg), cytogenetic responses were seen in 53% of patients, with 13% achieving a complete cytogenetic response. Side effects have been minimal with no dose-limiting toxicities encountered. The most common side effects have been nausea, vomiting, fluid retention, muscle cramps, and arthralgias. Grades 2 and 3 myelosuppression were observed at a dose >300 mg in 21% and 8% of patients, respectively. The myelosuppression might be consistent with a therapeutic effect as most of the hematopoiesis in these patients is contributed by the Ph(+) clone. Pharmacokinetic studies showed that the half-life of STI571 is 13–16 hours, which is sufficiently long to permit once daily dosing. Although the follow-up on this group of patients is relatively short, these data indicate that an Abl-specific tyrosine kinase inhibitor has significant activity in CML, even in IFN refractory patients. This trial also demonstrates the essential role of Bcr-Abl tyrosine kinase activity in CML.

Given the effectiveness of STI571 in chronic phase patients who had failed IFN, the Phase I studies were expanded to include CML patients in myeloid and lymphoid blast crisis and patients with relapsed or refractory Ph(+) ALL.[31] Patients have been treated with daily doses of 300–1,000 mg of STI571. Fifty-five percent (21/38) of patients with myeloid blast crisis responded to therapy, defined by a decrease in percentage of marrow blasts to less than 15%, and 21% (8/38) had clearance of blasts from their marrows to less than or equal to 5%. Seventy percent (14/20) of patients with lymphoid phenotype disease, CML in lymphoid blast crisis, or Ph(+) ALL responded, with 55% (11/20) clearing their marrow blasts to 5 %. Unfortunately, all but one of the lymphoid phenotype patients relapsed between days 42 and 123. However, 18% (7/38) of the myeloid blast crisis patients continue on STI571, in remission, with follow-up ranging from 101 to 349 days. Thus, STI571 has remarkable single agent activity in CML blast crisis and Ph(+) ALL, but responses tend not to be durable. However, these studies

demonstrate that in the majority of cases, the leukemic clone in Bcr-Abl-(+) acute leukemias, including CML blast crisis, remains at least partially dependent on Bcr-Abl kinase activity for survival.

The success of the Phase I studies prompted Phase II studies; single agent STI571 was tested further in interferon-refractory and interferon-intolerant patients as well as accelerated phase patients and patients with CML in myeloid blast crisis and Ph(+) ALL. These studies accrued more than 1,000 patients at 27 centers in 6 countries over a period of 6–9 months, and interim results from these studies were presented at the American Society of Hematology meeting in December 2000.[32-34] The results of these studies confirmed the results seen in the Phase I trials and served as the basis for accelerated FDA approval of STI571. A Phase III randomized study comparing STI571 with interferon plus cytarabine in newly diagnosed patients accrued over 1,000 patients in a 6-month period, and data collection is ongoing.

LESSONS LEARNED FROM DEVELOPMENT OF A GENE-TARGETED THERAPEUTIC AGENT

The results seen to date with STI571 confirm the role of Bcr-Abl and the importance of tyrosine kinase activity in the pathogenesis of CML. In addition, the activity of STI571 in blast crisis patients confirms that the malignant clone remains at least partially dependent on Bcr-Abl kinase activity for survival. From these Phase I studies, it is clear that durability of responses is greater earlier in the course of the disease—that is, chronic phase vs blast crisis of CML. This suggests that even better results might be seen if STI571 is used to treat patients earlier in the course of the disease—those who are newly diagnosed. In a subset of these patients, *bcr-abl* might be the sole molecular abnormality, and conceivably STI571 could be capable of eradicating the malignant clone. With disease progression, other molecular abnormalities are likely present and may be responsible for mediating resistance. Other mechanisms of resistance that might be operative with a gene-targeted therapeutic agent include target gene amplification,[35,36] *bcr-abl* mutation,[37] or overexpression of multidrug resistance protein.[38] Evaluation of mechanisms of relapse using patient samples is ongoing.

Preclinical data demonstrates that the addition of STI571 to other antileukemic agents such as cytarabine, IFN-α, or daunorubicin has an enhanced antiproliferative effect.[39,40] A combination of STI571 with these conventional antileukemic agents may be useful to improve the durability of responses seen in patients with advanced disease by avoiding in vivo selection of CML clones harboring additional genetic abnormalities. However, the ultimate goal of combination therapy would be to further improve the rate and durability of complete cytogenetic responses in patients with chronic phase CML. Clinical trials using STI571 in combination with IFN and with low-dose cytarabine are ongoing in chronic phase patients. For blast crisis and Ph(+) ALL, STI571 is being tested in combination with standard induction chemotherapy regimens.

Another important issue in the development of gene-targeted therapeutics is that of ideal dosing. Unlike conventional chemotherapeutic agents, maximum tolerated dose may not be relevant, and minimally effective dose may represent suboptimal use of agents such as STI571.[41] With STI571, in vitro studies revealed maximal effect at 1 μM, and remarkable clinical efficacy was seen when 1 μM through levels were achieved. Ideally, dosing of STI571 should strive for maximal kinase inhibition, and studies are underway in our laboratory to correlate conventional pharmacokinetic data with molecular assays of target effect (kinase inhibition) and, more importantly, with outcome and therapeutic effect. These data, combined with rapidly advancing technology in the measurement of minimal residual disease in CML, should allow for optional utilization of a gene product targeted therapeutic such as STI571 beyond that which is found in the realm of conventional chemotherapeutics.

FUTURE DIRECTIONS

The success of STI571 has engendered significant debate about how best to integrate such therapy into current treatment algorithms. The long-term efficacy of the compound is unknown, and the possibility of sustained tyrosine kinase inhibition leading to complete disease eradication may offer clear alternatives to current standards. For patients trying to decide between available options, such as allogeneic stem cell transplant vs STI571, current algorithms such as those used to decide between interferon and allogeneic transplant should be incorporated with careful assessment of prognostic factors and therapeutic risks. Despite the curative potential of allogeneic stem cell transplant, the emergence of more favorable nontransplant therapies may make physicians and patients less willing to accept the risks of transplant.

OTHER THERAPEUTIC TARGETS FOR STI571

Although STI571 was tested as a treatment for Bcr-Abl-associated leukemias, its original target was the PDGFR, and it was subsequently shown to inhibit the *c-kit* tyrosine kinase. Thus, STI571 should also have activity in diseases associated with constitutive activation of these kinases. In the case of *c-kit*, activating mutations are associated with gastrointestinal stromal tumor (GIST),[42,43] which is highly refractory to chemotherapy. Results from an ongoing Phase I study using STI571 to treat patients with GIST have shown response rates close to 60%.[44,45] A particularly interesting finding from this study is that activating mutations of *c-kit* correlated with response, whereas patients expressing wild-type *c-kit* had a significantly lower response rate.[44] This suggests that other tumors where *c-kit* is expressed but not activated by mutation may also be less likely to respond to STI571. Tumors that express *c-kit* include germ cell tumors, small-cell lung cancer (SCLC), AML, neuroblastoma, melanoma, ovarian cancer, and myeloma. Approximately 70% of SCLCs express *c-kit* and its ligand

stem cell factor, potentially establishing an autocrine growth loop. STI571 has been shown to inhibit growth of SCLC cell lines but required a relatively high concentration of STI571 for inhibition of cellular growth with an IC50 of approximately 5 mmolL.[46,47] Studies are ongoing with STI571 to determine whether tumors that express *c-kit* will respond to STI571.

The majority of cases of systemic mastocytosis have a mutation of aspartic acid 816 to valine (D816V) in the kinase domain of *c-kit*, resulting in activation of *c-kit*. Unfortunately, the kinase activity of the D816V mutant isoform has been recently shown to be resistant to STI571.[48] Thus, STI571 is unlikely to be useful in this disorder.

With respect to PDGFR as a target, a subtype of chronic myelomonocytic leukemia (CMML) has a constitutively active Tel-PDGFR fusion protein tyrosine kinase as a consequence of a (5;12) translocation.[49] STI571 has shown in vitro inhibition of leukemic cell lines expressing Tel-PDGFR and may be useful in patients with CMML and t(5;12).[27] Glioblastoma, the most common brain tumor and a highly chemotherapy and radiation resistant tumor, is associated with an autocrine growth loop involving PDGF and its receptor. STI571 has been shown to inhibit the growth of glioblastoma cells injected into the brains of nude mice, suggesting that this agent could have potential as therapy for this currently incurable disease.[50] Numerous other malignancies have also been reported to have autocrine activation of PDGFR, including non-small–cell lung cancer, breast cancer, prostate cancer, and a variety of sarcomas; however, the data supporting a role for PDGFR activation in these diseases is less compelling.[51] Nevertheless, we envision that for these diseases clinical trials with STI571 could be performed to test this hypothesis. However, it is unlikely that a defect in a single protein kinase is responsible for malignant transformation in most of the aforementioned tumors, and, therefore, it is unreasonable to expect results as dramatic as those seen in the treatment of CML when using STI571 alone for these other indications. Greater efficacy may be expected when the kinase inhibitor is used in combination with chemotherapy or even with other molecularly targeted therapies. Lastly, PDGFR activation may have a role in a variety of fibrotic disorders such as myelofibrosis, pulmonary fibrosis, and hepatic fibrosis.[52] Given the acceptable toxicity profile, an exploration of the activity of STI571 in these disorders may also be warranted.

CONCLUSIONS

STI571 is an example of a rationally designed, molecularly-targeted therapy based on the specific abnormality present in a human malignancy. Although it promises to be an important advance in the treatment of CML, its successful development represents a new paradigm in cancer drug development, which will hopefully be followed by other specific targeted therapies in oncology. **OS**

REFERENCES

1. Kolibaba KS, Druker BJ. Current status of treatment for chronic myelogenous leukemia. *Medscape Oncology*. 2000;3.
2. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340:1330–1340.
3. Faderl S, Talpaz M, Estrov Z, et al. Chronic myelogenous leukemia: biology and therapy. *Ann Intern Med*. 1999;131:207–219.
4. Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science*. 1960;132:1497–1501.
5. Rowley JD. A new consistent abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and giemsa staining. *Nature*. 1973;243:290–293.
6. de Klein A, Geurts van Kessel A[AU: name correct?], Grosveld G, et al. A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukemia. *Nature*. 1982;200:765-767.
7. Heisterkamp N, Stephenson JR, Groffen J, et al. Localization of the c-abl oncogene adjacent to a translocation break point in chronic myelocytic leukemia. *Nature*. 1983;306:239–242.
8. Shtivelman E, Lifshitz B, Gale RP, et al. Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. *Nature*. 1985;315:550–554.
9. Melo JV. The molecular biology of chronic myeloid leukemia. *Leukemia*. 1996;10:751–756.
10. Abelson HT, Rabstein LS. Lymphosarcoma: virus-induced thymic-independent disease in mice. *Cancer Res*. 1970;30:2213–2222.
11. Witte ON, Dasgupta A, Baltimore D. Ableson murine leukemia virus protein is phosphorylated in vitro to form phosphoprotein. *Nature*. 1980;283:826–831.
12. Witte ON, Goff S, Rosenberg N, et al. A transformation-defective mutant of Abelson murine leukemia virus lacks protein kinase activity. *Proc Natl Acad Sci USA*. 1980;77:4993–4997.
13. Lugo TG, Pendergast AM, Muller AJ, et al. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. *Science*. 1990;247:1079–1082.
14. McLaughlin J, Chianese E, Witte ON. In vitro transformation of immature hematopoietic cells by the P210 BCR/ABL oncogene product of the Philadelphia chromosome. *Proc Natl Acad Sci USA*. 1987;84:6558–6562.
15. Gishizky ML, Witte ON. Initiation of deregulated growth of multipotent progenitor cells by bcr-abl in vitro. *Science*. 1992;256:836–839.
16. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science*. 1990;247:824–830.
17. Kelliher MA, McLaughlin J, Witte ON, et al. Induction of a chronic myelogenous leukemia-like syndrome in mice with v-abl and BCR/ABL. *Proc Natl Acad Sci USA*. 1990;87:6649–6653.
18. Heisterkamp N, Jenster G, ten Hoeve J, et al. Acute leukaemia in bcr/abl transgenic mice. *Nature*. 1990;344:251–253.
19. Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. *Blood*. 2000;96:3343–3356.
20. Yaish P, Gazit A, Gilon C, et al. Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. *Science*. 1988;242:933–935.
21. Anafi M, Gazit A, Zehavi A, et al. Tyrphostin-induced inhibition of p210bcr-abl tyrosine kinase activity induces K562 to differentiate. *Blood*. 1993;82:3524–3529.
22. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the ABL tyrosine kinase on the growth of BCR-ABL positive cells. *Nature Med*. 1996;2:561–566.
23. Marley SB, Deininger MW, Davidson RJ, et al. The tyrosine kinase inhibitor STI571, like interferon-alpha, preferentially reduces the capacity for amplification of granulocyte-macrophage progenitors from patients with chronic myeloid leukemia. *Exp Hematol*. 2000;28:551–557.
24. Deininger MW, Goldman JM, Lydon N, Melo JV. The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells. *Blood*. 1997;90:3691-3698.
25. Kasper B, Fruehauf S, Schiedlmeier B, et al. Favorable therapeutic index of a p210(BCR-ABL)-specific tyrosine kinase inhibitor; activity on lineage-committed and primitive chronic myelogenous leukemia progenitors. *Cancer Chemother Pharmacol*. 1999;44:433–438.
26. Gambacorti-Passerini C, le Coutre P, Mologni L, et al. Inhibition of the ABL kinase activity blocks the proliferation of BCR/ABL+ leukemic cells and induces apoptosis. *Blood Cells Mol Dis*. 1997;23:380–394.

27. Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL and TEL-PDGFR fusion proteins. *Blood*. 1997;90:4947–4952.
28. Beran M, Cao X, Estrov Z, et al. Selective inhibition of cell proliferation and BCR-ABL phosphorylation in acute lymphoblastic leukemia cells expressing Mr 190,000 BCR-ABL protein by a tyrosine kinase inhibitor (CGP-57148). *Clin Cancer Res*. 1998;4:1661–1672.
29. le Coutre P, Mologni L, Cleris L, et al. In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. *J Natl Cancer Inst*. 1999;91:163–168.
30. Druker BJ, Talpaz M, Resta D, et al. Efficacy and safety of a specific inhibitor of the Bcr-Abl tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344:1031–1037.
31. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the Bcr-Abl tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med*. 2001;344:1038–1042.
32. Kantarjian H, Sawyers C, Hochhaus A, et al. Phase II study of STI571, a tyrosine kinase inhibitor, in patients with resistant or refractoryPhiladelphia chromosome positive chronic myeloid leukemia. *Blood*. 2000;96:470a.
33. Sawyers CL, Hochhaus A, Feldman E, et al. A Phase II study to determine the safety and anti-leukemic effects of STI571 in patients with Philadelphia chromosome positive chronic myeloid leukemia in myeloid blast crisis. *Blood*. 2000;96:503a.
34. Talpaz M, Silver RT, Druker BJ, et al. A Phase II study of STI571 in adult patients with Philadelphia chromosome positive chronic myeloid leukemia in accelerated phase. *Blood*. 2000;96:469a.
35. le Coutre P, Tassi E, Varella-Garcia M, et al. Induction of resistance to the Abelson inhibitor STI571 in human leukemic cells through gene amplification. *Blood*. 2000;95:1758–1766.
36. Weisberg E, Griffin JD. Mechanism of resistance to the ABL tyrosine kinase inhibitor STI571 in BCR/ABL-transformed hematopoietic celllines. *Blood*. 2000;95:3498-3505.
37. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science*. 2001;293:876-880.
38. Mahon FX, Deininger MW, Schultheis B, et al. Selection and characterization of BCR-ABL positive cell lines with differential sensitivity to the tyrosine kinase inhibitor STI571: diverse mechanisms of resistance. *Blood*. 2000;96:1070–1079.
39. Thiesing JT, Ohno-Jones S, Kolibaba KS, et al. Efficacy of an Abl tyrosine kinase inhibitor in conjunction with other anti-leukemic agents against Bcr-Abl positive cells. *Blood*. 2000;96:3195–3199.
40. Fang G, Kim CN, Perkins CL, et al. CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl-positive human leukemia cells to apoptosis due to antileukemic drugs. *Blood*. 2000;96:2246–2253.
41. Druker BJ, Lydon NB. Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. *J Clin Invest*. 2000;105:3–7.
42. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science*. 1998;279:577–580.
43. Lux ML, Rubin BP, Biase TL, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol*. 2000;156:791–795.
44. Blanke CD, von Mehren M, Joensuu H, et al. Evaluation of the safety and efficacy of an oral molecularly-targeted therapy, STI571, in patients with unresectable or metastatic gastrointestinal stromal tumors (GISTS) expressing c-KIT (CD117). *Proc Am Soc Clin Oncol*. 2001;20:1a.
45. Van Oosterom AT, Judson I, Verweij J, et al. STI571, an active drug in metastatic gastrointestinal stromal tumors (GIST), an EORTC Phase I study. *Proc Am Soc Clin Oncol*. 2001;20:1a.
46. Krystal GW, Honsawek S, Litz J, et al. The selective tyrosine kinase inhibitor STI571 inhibits small cell lung cancer growth. *Clin Cancer Res*. 2000;6:3319–3326.
47. Wang WL, Healy ME, Sattler M, et al. Growth inhibition and modulation of kinase pathways of small cell lung cancer cell lines by the novel tyrosine kinase inhibitor STI 571. *Oncogene*. 2000;19:3521–3528.
48. Heinrich MC, Wait CL, Yee KWH, et al. STI571 inhibits the kinase activity of wild type and juxtamembrane c-kit mutants but not the exon 17 D816V mutation associated with mastocytosis. *Blood*. 2000;96:173b.
49. Golub TR, Barker GF, Lovett M, et al. Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. *Cell*. 1994;77:307–316.
50. Kilic T, Alberta JA, Zdunek PR, et al. Intracranial inhibition of platelet-derived growth factor-mediated glioblastoma cell growth by an orally active kinase inhibitor of the 2-phenylaminopyrimidine class. *Cancer Res*. 2000;60:5143–5150.
51. Kolibaba KS, Druker BJ. Protein tyrosine kinases and cancer. Biochimica et *Biophysica Acta*. 1997;1333:F217–F248.
52. Ostman A, Heldin CH. Involvement of platelet-derived growth factor in disease: development of specific antagonists. *Adv Cancer Res*. 2001;80:1–38.