When I was a youngster in Illinois in the 1950s, the world of sport was shocked by the feat of Roger Bannister, now a distinguished neurologist, but then an Oxford medical student who did the impossible. On May 6, 1954 he broke the four-minute barrier in the mile (Fig. 1). While improving upon the world record by only a few seconds, he changed the complexion of distance running in a single afternoon. A combination of exceptional training, perfect conditions, better equipment, and extraordinary human effort opened the floodgates to other milers, marathoners, and sprinters. Track records fell like ripe apples in the late 50s and 60s. Will the same happen in the field of cancer treatment?

This issue of The Oncologist contains a memorable article by Brian Druker’s group at Oregon Health Sciences, summarizing their experience with the remarkable new drug, Gleevec™ (STI571) in chronic myelogenous leukemia (CML) [1]. It follows a series of papers in The New England Journal of Medicine in April 2001, detailing remarkable activity in CML and in gastrointestinal stromal tumors (GIST) [2, 3, 4]. In this issue of The Oncologist Mauro and Druker present previously unpublished information regarding the drug’s pharmacokinetics: its reliable absorption, long half-life, and limited acute and chronic toxicity [1]. Taken together, this information about efficacy, toxicity, and pharmacokinetics leads to the conclusion that this drug is a paradigm for the ideal molecularly targeted drug. At this juncture it is useful to reflect on its importance to the field of cancer chemotherapy and drug discovery.

Prior to the era of molecular oncology, the understanding of cancer biology was largely descriptive and quantitative: cancer cells grew faster than normal cells, invaded adjacent tissue, metastasized, and mutated. The reasons for these differences in behavior between normal and malignant cells were largely unexplained, and the development of therapies was therefore empirical. In the 1970s, the process of malignant transformation began to yield its secrets in molecular terms, with the discovery of oncogenes such as ras, and later suppressor genes, mutated growth factor receptors, over-expressed signaling pathways, and mutated transcription factors. Faced with this abundance of information about how cells become malignant, it was only logical to propose that these changes could become targets for chemotherapy. This possibility led to wholesale changes in screening programs at the National Cancer Institute and in industry, and to the growth of a number of new biotechnology companies, each with its own targets and animal models of human cancer.

What has been accomplished? The practice of molecular targeted drug discovery proved much more complex and unrewarding than initially imagined. Perhaps the most visible early attempt, the inhibition of ras through inhibition of its farnesylation, failed to yield a drug effective against pancreatic cancer and other solid tumors that contain mutated and activated ras. The reasons for failure of this class of inhibitors in trials against solid tumors are still uncertain [5, 6]. There were conceptual flaws. The farnesyl transferase inhibitors were not specific for ras, but inhibited farnesylation of multiple other proteins. They were not as effective against k-ras, the predominant form of the oncogene in human tumors, as against h-ras. Trials continue with alternative schedules and against other tumors, including leukemias, but at this point, the ras inhibitors do not look promising.

Serendipity has proven more successful. Among the most promising targets are translocations that alter proliferation or maturation of hematopoietic cells. The 15:17 translocation...
in acute promyelocytic leukemia decreases affinity of the retinoic acid receptor component, RXR, for retinoids, leading to a block in retinoid binding and cell differentiation. High doses of all-trans retinoic acid (ATRA) effectively overcome the block and, in conjunction with chemotherapy, promise to cure most patients with this disease. However, the first use of ATRA in China almost 15 years ago was prompted not by molecular considerations but by the drug’s availability and its known differentiating effects on other tissues. Only in retrospect was the mechanism of action appreciated.

Thus we come to STI571, selected as an inhibitor of the bcr-abl kinase, the activated oncogene product in CML. Why does it succeed where others have failed? Probably the most important factor is the bcr-abl kinase: this protein is the product of a single mutation that is overexpressed in virtually all CML cases, and it is both necessary and sufficient to create the disease, and is essential for survival of the malignant cells [7]. The bcr-abl kinase is a promoter of proliferation and an inhibitor of apoptosis. Without it, CML cells die. This essential feature of the target distinguishes it from the complex series of mutations that lead to solid tumors in man. In tumors such as colon cancer, no single step, as yet identified, is both necessary for initiation of the malignancy and essential for its further progression. It is telling that STI571, although effective against GIST, produces partial responses in perhaps 50% of these tumors, primarily in those that strongly overexpress c-kit; perhaps the c-kit overexpression in these tumors is only a contributing factor, and only one of several mutations leading to malignant progression in this class of tumors. Perhaps further efforts at molecularly targeted therapy will be most effective against those few malignancies where a single translocation or activating mutation leads to cancer; unfortunately, the best examples are relatively uncommon leukemias.

Another factor accounting for the success of STI571 is its very favorable pharmacologic features: high degree of specificity for its target (and therefore low toxicity for normal tissues), excellent pharmacokinetics, and strongly favorable therapeutic ratio of efficacy to toxicity. While not a particularly potent inhibitor of the bcr-abl kinase (IC-50 of 0.1 µM) it is highly selective, its only other targets being c-kit and platelet-derived growth factor (PDGF) receptor. This fortunate constellation of properties has led to success.

Are there problems ahead for STI571? We still do not know whether CML control is permanent or temporary. Will STI571 simply prolong the interval from diagnosis to blastic transformation, or will it control the disease permanently? Most patients do not achieve a molecular remission or even normal cytogenetics. In most cases of cancer where tumor cells are left behind, relapse is likely. Resistance, while not seen in chronic phase CML patients to this date, is still a possibility, and indeed resistance is a reality in blastic transformation. Mechanisms of resistance in man are poorly understood, but the possibilities are manifold [8]. STI571 is a substrate for the multi-drug resistance transporter. It selects for bcr-abl amplified cells in tissue culture. It could certainly fall prey to changes in apoptosis.

What are the opportunities? It should and will be tested against other tumors expressing c-kit and PDGF receptor, and is likely to work against chronic monomyelocytic leukemia, in which the c-kit receptor is overexpressed. Trials are under way in prostate cancer, lung cancer, gliomas, and in other tumors overexpressing PDGF receptor or c-kit. Certainly, as an anti-apoptotic factor, it is inviting to use the drug in combination with chemotherapy, both in chronic phase and in blastic crisis of CML [9]. Perhaps it can produce the molecular cures in chronic phase and permanent remissions in blastic phase now unlikely or impossible with single-agent treatment. Perhaps it will be dramatically more effective when used with hormonal therapy against prostate cancer, which overexpresses PDGF receptor, or with chemotherapy against gliomas, which overexpress the same protein [10]. Would a multidrug resistance inhibitor enhance its effectiveness against solid tumors? We have only begun to explore these possibilities.

In conclusion, STI571, or Gleevec™, represents a monumental leap forward in cancer chemotherapy. It proves a principle. It justifies an approach. It demonstrates that highly specific, non-toxic therapy is possible. It does not guarantee success of similar efforts, because CML may not be typical of most other malignancies. And we have much to learn about maximizing its value. Congratulations to Novartis, to Brian Druker, and their colleagues for accomplishing the equivalent of the 4-minute mile (Fig. 2). To their colleagues in the fight against cancer, are the floodgates finally open?

Figure 2. Dr. Brian J. Druker in Duniway Park, Portland, Oregon.
REFERENCES


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On page 231, the target protein for ATRA should read, “…the fusion PML-RAR protein.”
In the next to last paragraph, because STI571 induces programmed cell death, it should read, “Since the bcr-abl protein is anti-apoptotic, while the drug is pro-apoptotic, …”

On page 8, in the second paragraph from the bottom under **Randomized Phase III Trials of Paclitaxel Plus Doxorubicin in MBC**, doxorubicin was erroneously called docetaxel: “… or a combination of 50 mg/m² docetaxel and 150 mg/m² paclitaxel, again over 24 hours” should be “or a combination of 50 mg/m² doxorubicin and 150 mg/m² paclitaxel, again over 24 hours.”