

Protein tyrosine kinase inhibitors: new treatment modalities?

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Protein tyrosine kinases (PTKs) have been recognized as attractive cell-signaling targets for drug discovery in the treatment of cancer and other diseases. Most of the PTK inhibitors are small molecules, designed to compete for, or nearby, the ATP-binding site, and are currently in phase I–III clinical trials, mainly for oncological indications. Recent efforts focused on the synthesis of selective PTK inhibitors have generated several promising clinical candidates, which recently culminated in the approval of Gleevec™, the first kinase inhibitor registered for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors.

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Current Opinion in Pharmacology 2002, 2:374–381

1471-4892/02/\$ – see front matter

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Abbreviations

AML	acute myeloid leukemia
CML	chronic myeloid leukemia
EGF-R	epidermal growth factor receptor
GIST	gastrointestinal stromal tumor
mAb	monoclonal antibody
PDGF-R	platelet-derived growth factor receptor
PTK	protein tyrosine kinase
RPTK	receptor PTK
VEGF	vascular endothelial growth factor
VEGF-R	VEGF receptor

Introduction

Today, the identification and development of therapeutic agents for disease states linked to the overexpression or abnormal activation of protein tyrosine kinases (PTKs) has become a major field of research in both academic institutions and pharmaceutical companies. Several medicinal chemistry approaches have been pursued to inhibit the various PTKs that are deregulated in different human diseases. In the past few years, tremendous progress has been made with respect to the preclinical and clinical development of PTK inhibitors, which is reflected in the fact that several ATP-site-directed PTK inhibitors are now in advanced stages of clinical trials, or have already been approved (Table 1). This review focuses mainly on the development of small-molecule inhibitors, with special emphasis on imatinib (known as Gleevec™ in the USA and Glivec® elsewhere; Novartis, Basel, Switzerland). In addition, issues related to the preclinical and clinical development of PTK inhibitors are addressed.

What is the status of protein tyrosine kinase inhibitors today?

Rationale for targeting protein tyrosine kinases

It is now well established that PTKs play a crucial role in signal transduction pathways that regulate several cellular

functions, under both normal conditions and deregulated conditions [1•–5•]. Consequently, an ever-increasing number of PTKs have been selected as molecular targets, following the initial drug discovery programs that were instigated around a few PTK targets 15 years ago (Table 1; [6–8,9•,10•]). PTKs were mainly selected as prime targets for the development of anticancer agents because, in several cancers, their activity was found to be upregulated by gain-of-function mutations or overexpression. PTK activity can be upregulated by several mechanisms: by genomic rearrangements, for example, Bcr–Abl in chronic myeloid leukemia (CML) [11]; by point mutations in frame deletions or insertions, for example, Flt-3 in acute myeloid leukemia (AML) and c-Kit (the receptor for stem-cell factor) in gastrointestinal stromal tumors (GISTs) [12•,13,14•]; overexpression, for example, epidermal growth factor receptor (EGF-R) and HER2 in various carcinomas [15•,16]; and ectopic or unscheduled expression of growth factors such as vascular endothelial growth factor (VEGF) and its receptors on endothelial cells, which are responsible for the induction of tumor and lymph angiogenesis [9•,17•,18,19]. The recent sequencing of the human genome revealed that the kinome contains ~500 human protein kinase genes, of which more than 90 are PTKs [1•]. In particular, the receptor PTKs (RPTKs) have attracted a lot of attention because their ligand-inducible PTK activity in untransformed cells is normally tightly regulated but, when mutated or altered structurally, the RPTKs can become transforming. In fact, more than 50% of the known RPTKs have been repeatedly found to be either mutated or overexpressed in association with human malignancies [1•–3•,7,8]. Of the 30 RPTKs that have been implicated in human solid cancers, the deregulation of the EGF-R and VEGF receptor (VEGF-R) systems appears to be most prevalent in various carcinomas and has been, and still is, the subject of many inhibitor programs (Tables 1 and 2). Similar to the serine-specific and threonine-specific kinases, the utility of PTK inhibitors, as anti-angiogenic drugs in particular, is being explored in several non-malignant conditions, including rheumatoid arthritis, psoriasis, diabetic retinopathy and possibly contraception (Table 1, [17•,18,19]).

Rationale for targeting the ATP binding site

Initially, the inhibition of PTKs by compounds directed to the ATP-binding site was considered less attractive than substrate-based inhibitors due, among other factors, to the belief that because the catalytic domain is highly conserved across protein kinases, it would be very difficult to design selective ATP-competitive inhibitors. However, the synthesis of low-molecular-weight compounds capable of interfering with ligand binding (in the case of RPTKs) or targeting regulatory hypervariable sequences responsible for substrate binding has proven to be extremely difficult [20,21•].

Table 1**Protein kinase inhibitors in clinical trials.**

Inhibitor	Company	Target kinase(s)	Status
Flavopiridol	Aventis	Cdks	Phase II
CI 1040	Pfizer	MEK	Phase I
RAD001	Novartis	mTOR	Phase I
CCI779	Wyeth-Ayerst	mTOR	Phase II
E7070	Eisai	Cdks	Phase I
Cyc202	Cyclacel	Cdks	Phase I
Bryostatin-I	Bristol Myers Squibb	PKC	Phase I–II
PKC412	Novartis	PKC and VEGF	Phase I/IIA for retinopathy
UCN-01	NCI	PKC and Chk1	Phase I
ISIS 3521 (antisense)	ISIS	PKC- α	Phase I/II
GEM231 (antisense)	Hybridon	PKA	Phase I
BIRB0796	Boehringer Ingelheim	p38	Phase II
SCIO-469	Scios	p38	Phase I
BAY 43-9006	Bayer	c-raf	Phase I
CEP-1347	Cephalon	Jun	Phase I
LY-333531	Eli Lilly	PKC- β	Phase II/III for retinopathy
Imatinib	Novartis	Abl (c-Kit, PDGF-R)	Phase III; FDA approval 5/01 for CML and 2/02 for GISTs
PKC412	Novartis	Flt-3	Phase I for AML
PTK787/ZK222584	Novartis/Schering AG	KDR	Phase I
PKI166	Novartis	EGF-R and HER-2	Phase I
AG013726	Agouron	VEGF-R2, PDGF-R	Phase I
KRN633	Kirin	VEGF-R1/2, Kit	Phase I
CHIR 200131	Chiron	VEGF-R1/2, FGF-R, PDGF-R	Phase I
OSI-774 (Tarceva™)	Roche/Genentech/OSI	EGF-R	Phase III
CI-1033 (irreversible)	Pfizer/Warner-Lambert	EGF-R and HER-2	Phase I
CP-547632	Pfizer	VEGF-R2, FGF-R	Phase I
EKB-569	Wyeth-Ayerst	EGF-R and HER-2	Phase I
GW-2016	GlaxoSmithKline	EGF-R and HER-2	Phase I
SU5416	SUGEN/Pharmacia	KDR	Phase III
SU6668	SUGEN/Pharmacia	KDR (PDGF-R, FGF-R)	Phase I
SU11248	SUGEN/Pharmacia	PDGF-R	Phase II
ZD 6474	AstraZeneca	KDR and EGF-R	Phase I
ZD 1839 (Iressa™)	AstraZeneca	EGF-R	Phase III
CEP-701	Cephalon	Trk	Phase II
Angiozyme®	Ribozyne	VEGF-R1 (Flt-1)	Phase II

Cdk, cyclin-dependent kinase; Chk1, checkpoint kinase 1; Cyc, cyclin epidermal growth factor; FGF-R, fibroblast growth factor receptor; KDR, kinase domain receptor (also called VEGF-R2); MEK, mitogen-activated protein kinase kinase; PKA, protein kinase A; PKC, protein kinase C.

Similarly, the design of small-molecule ligands to inhibit the binding of specific phosphotyrosine-containing peptides to SH2 domains, thereby interrupting tyrosine kinase signaling, have failed despite considerable efforts and significant advances [22*,23*]. Thus far, the only successful agents that inhibit PTKs without targeting the ATP-binding sites are the monoclonal antibodies (mAbs) such as trastuzumab (Herceptin®; Genentech Inc., San Francisco, CA, USA; Table 2). These antibody-based approaches have clearly demonstrated, both preclinically and clinically, that the inhibition of PTKs as a strategy to inhibit cancer growth is feasible, and they have paved the way for developing less expensive and less complex low-molecular-weight PTK inhibitors.

Issues relating to targeting of the ATP-binding site

Although the targeting of the ATP-binding site of PTKs appears to be the most promising approach for drug intervention, two major obstacles must be overcome: access to the intracellular targets and selectivity. Considering the fact that there are as many as 500 protein kinases [1**,24],

it is not surprising that selectivity has proved to be the more difficult of the two problems to solve. Progress has been made recently in the successful crystallization of protein kinases bound to ATP analogs and/or PTK inhibitors. This structure-based approach has confirmed that the ATP-binding domain is conserved within the protein kinase family and that the architecture in the proximal region does afford some key diversity [8,10*,25**,26,27]. However, the quest for the holy grail of kinase inhibition — namely the identification of a single agent that specifically targets a single kinase out of the whole human kinome — will probably remain a dream. Therefore, the emphasis has been transferred to molecules that possess inhibitory profiles with an acceptable safety margin in clinical trials.

Validation of concept for protein tyrosine kinase inhibitors

The recent development of a range of relatively selective protein kinase inhibitors shows that inhibition of a deregulated protein kinase activity is sufficient to inhibit tumor

Table 2**Antibody protein kinase inhibitors in clinical trials.**

Antibody	Company	Target kinase(s)	Status
IMC-225 (Erbix™, cetuximab)	ImClone and Merck KGaA	Chimeric mAb against EGF-R	Phase II/III (colon, H&N, pancreas and renal cancer) Combination with CPT-11 (irinotecan), paclitaxel (breast), gemcitabine (pancreas), radiation (H&N)
Trastuzumab	Genentech	Humanized mAb against HER-2	FDA approval for advanced breast cancer Phase IV
Bevacizumab (Avastin™, RhuMab)	Genentech	Humanized mAb against VEGF	Phase II (breast, prostate). Combination with carboplatin/paclitaxel (NSCLC), 5FU/leucovorin (colon cancer)
ABX-EGF	Abgenix/Immunex	Humanized mAb against EGF-R	Phase II (kidney and lung cancer)
MDX-447 (EMD 82633)	Medarex	Humanized mAb against EGF-R	Phase II
MV833	EORTC	Humanized mAb against VEGF-R	Phase I
IMC-1C11	ImClone	Chimeric mAb against VEGF-R	Phase I
CDP 860	Celltech	Humanized mAb against PDGF-R	Phase I

H&N, head and neck cancer; NSCLC, non-small-cell lung cancer; 5FU, 5-fluorouracil.

growth. This has turned the step-wise concept validation for PTK inhibition — from the biochemical, cellular and animal levels to proof of concept in the clinic — into a reality (Tables 1 and 2; [8,9^{••},10[•],26,27]). Although the preclinical *in vitro* and *in vivo* validation of the concept has been achieved relatively easily, proof in the clinic that the inhibition of the targeted protein kinase leads to, or is associated with, the inhibition of tumor growth (in particular in solid tumors) is much more difficult to obtain. An additional level of complexity is to prove that inhibition of the targeted PTK within the tumor is associated with anti-tumor activity. This antitumor activity should ideally occur only in the patient population that demonstrates the presence of the target in the tumor and would therefore be expected to respond to the treatment. Finally, it would be highly desirable to directly determine the levels of inhibition of the targeted PTK in the tumor, as such proof of pharmacodynamic endpoints will be key in defining a pharmacologically relevant dose in the clinic.

The potentials and limitations of the prototype protein tyrosine kinase inhibitor imatinib

The clinical efficacy of imatinib

Imatinib has demonstrated an impressive hematological and cytogenetic response in the chronic, accelerated and, to some extent, even in the blastic phase of CML [28[•],29[•],30]. It has also shown significant clinical efficacy in the treatment of GISTs, which for poorly understood reasons are notoriously unresponsive to cancer chemotherapy [31[•],32^{••}]. The clinical efficacy of imatinib, which is linked to its excellent pharmacokinetic behavior combined with a protein kinase selectivity profile that resulted in good tolerability [30], has clearly demonstrated the potential for PTK inhibitors in cancer therapy.

Reasons for the clinical efficacy of imatinib

The well-defined pathogenetic events in CML and GISTs may represent a unique situation that explains the success of imatinib in this limited set of cancers. The Bcr–Abl fusion protein, which displays enhanced PTK activity, appears to be the major driving factor in the pathophysiology in most CML patients up to the blast crisis (reviewed

in [33[•]]). The fact that imatinib inhibits c-Kit was initially of concern, as this RPTK is the receptor for stem-cell factor and appears to play an important role in hematopoiesis [12[•],33[•]]. On the other hand, the deregulation of c-Kit associated with GISTs is due to gain-of-function mutations, resulting in a constitutive ligand-independent PTK activity, which appears to play a key role in the pathogenesis of this disease [12[•],33[•],34,35]. This is also reflected in the fact that tumor cells expressing abnormally active forms of Abl, c-Kit or the platelet-derived growth factor receptor (PDGF-R) are effectively killed or growth-arrested by imatinib, whereas the cellular counterparts expressing the normal version of these PTKs are spared (Table 3). Clinical responses in GIST patients following treatment with imatinib appear to be associated with the presence of gain-of-function mutations in c-Kit, as GIST patients expressing the wild-type version of c-Kit do not seem to respond to imatinib [12[•],33[•],34,35]. The fact that imatinib does not induce growth arrest and/or apoptosis in cells that express wild-type c-Abl, c-Kit or PDGF-R is poorly understood, but may be because the survival of tumor cells expressing the hyperactivated forms of these PTKs may become dependant on, or 'addicted' to, deregulated downstream signaling of these PTKs. This paradigm may be extended to other PTKs that are deregulated in tumors (reviewed in [1^{••}]). For example, in AML, about 30% of patients harbor a gain-of-function mutation in the Flt-3 gene, which hyperactivates this RPTK [13,14[•]]. Patients carrying these mutations in the Flt-3 gene have a poor clinical prognosis, suggesting that this RPTK may play a causative role in the progression of AML [13,14[•]]. Consequently, selective Flt-3 PTK inhibitors have been identified and phase I clinical trials in AML with these agents have been initiated ([36[•]]; Table 1).

Although responses of stable-phase CML to imatinib have, so far, been quite durable, most patients with blast-phase CML or Philadelphia chromosome positive (Ph⁺) acute lymphoblastic leukemia develop resistance to imatinib and relapse [37[•]]. The reasons for this resistance appear to be multiple, but data from recent clinical trials show that many relapsed patients (about 50%) carry point mutations (more

Table 3***In vitro* antiproliferative activity of imatinib.**

Cell line	Characteristics	Imatinib IC ₅₀ (μM)*
Ba/F3 +IL-3	Murine pre-lymphoid cells, IL-3 dependent	>10
Ba/F3-BcrAbl-wt without IL-3	Transformed by p210BcrAbl, IL-3 independent	<1
Ba/F3-BcrAbl-T315I	Transformed by p210BcrAbl with point mutation in Thr→315Ile, IL-3 independent	>10
Ba/F3-Tel-Abl	Transformed by Tel-Abl, IL-3 independent	<1
Ba/F3-Tel-PDGF-R	Transformed by Tel-PDGF-R, IL-3 independent	<1
K-562/ Ku-812F/ MEG-01	Human CML cell lines expressing p210BcrAbl	<1
32D + IL-3	Murine myeloid cells, IL-3 dependent	>10
32D-v-src	Murine myeloid cells, transformed by v-src, IL-3-independent	>10
32D-Bcr-Abl-wt	Murine myeloid cells, transformed by p210BcrAbl, IL-3 independent	<1
GIST882 without SCF	Human GIST cell expressing activating c-Kit mutation	<1
GIST780 without SCF	Human GIST cell expressing activating c-Kit mutation	<1
Balb/c 3T3	Mouse fibroblasts	>10
Balb/c v-sis	Mouse fibroblast transformed by v-sis	<1
Balb/c Ha-ras	Mouse fibroblast transformed by Ha-ras	>10
A10 + PDGF-BB	Smooth muscle cells stimulated by PDGF	<1
A10 + 10% FCS	Smooth muscle cells stimulated by 10% FCS	>10
T24	Human bladder carcinoma cells	>10
Colo 205	Human colon carcinoma cells	>10

*Antiproliferative activity (concentrations required to inhibit proliferation by 50%) was determined using standard antiproliferative assays. FCS, fetal calf serum; IL-3, interleukin-3; SCF, stem-cell factor.

than 12 mutations have been identified so far) in the kinase domain of Bcr–Abl, indicating that Bcr–Abl is indeed the target of imatinib in CML [37•,38•,39••,40•,41•]. Structural biology studies have provided evidence for the unusual binding mode of imatinib to Abl and have revealed how these point mutations can lead to resistance to imatinib [42••,43••]. Inhibitors targeting these imatinib-resistant forms of Bcr–Abl or signaling pathways downstream of Bcr–Abl may, therefore, represent new avenues for drug discovery to circumvent imatinib resistance. Whether similar resistance patterns to imatinib on c-kit will be generated in GIST remains to be seen.

In summary, although the full potential of imatinib has not yet been exploited in terms of treatment modality and indications — with reference in particular to other solid tumors that have deregulated c-Kit and PDGF-R — it is already apparent that resistance to TPK inhibitors will be observed in the future.

Which lessons, learned from imatinib, can be applied to other protein tyrosine kinase inhibitors?

Inhibitors of the epidermal growth factor receptor system

In contrast to GISTs and CML, a sizeable proportion of all solid tumors overexpress the normal forms of EGF-R and/or HER2 and, in a limited set of tumors, some mutated forms of EGF-R are found. This may lead to a variable degree of ligand-independent activation of their kinase activities via forced homodimerization and/or heterodimerization [1••,15•,16,44]. Nonetheless, inhibitors to these

RPTKs show broad-spectrum antitumor activity in animal models and single-agent activity in early-phase clinical trials in patients (Table 1; [44]). It is, therefore, not too surprising that the most common side effects (diarrhea and acne-like rash) in patients treated with the various RPTK inhibitors targeting the EGF-R/HER2 are mechanism based, and result from the inhibition of signaling pathway(s) that are present not only in the tumor but also in normal cells [44,45•]. In contrast to CML, where clinical efficacy of imatinib could be determined relatively rapidly, leading to the rapid assessment of a pharmacologically relevant dose, the measurements of clinical endpoints with RPTK inhibitors targeting EGF-R/HER2 and VEGF-R in solid tumors are more cumbersome. Although overexpression of EGF-R/HER2 usually correlates with poor prognosis, the stratification of patients likely to respond to these RPTK inhibitors has remained unsatisfactory. There are several reasons for this, including lack of suitable reagents (antibodies, tissue availability, etc.), lack of robust assays and tissue heterogeneity.

To cite one example, retrospective analysis attempting to relate clinical responses to the level of expression of HER2 in patients treated with trastuzumab is unconvincing [46••]. Similarly, determination of the optimal dose has been guided empirically, although data obtained in a recent study with ZD1839 (Iressa™; AstraZeneca, London, UK), support the notion for the requirement of pharmacodynamic assessments to select relevant doses and schedules, instead of the classical maximal-tolerated dose for definitive efficacy and safety trials [47].

Inhibitors of the vascular endothelial growth factor system

Similar dosing and, to some extent, safety issues have become apparent with PTK inhibitors targeted to VEGFs and their receptors, although the concept of inhibiting tumor angiogenesis by blocking VEGF signaling appears to be reasonably well proven at the preclinical level (reviewed in [19,48]). Both types of agents that target VEGF signaling (mAbs and the PTK inhibitors) have clearly demonstrated broad-spectrum antitumor activity in *in vivo* animal models (reviewed in [19,48]). In addition, early clinical trial data suggest that mAbs directed against VEGF are largely well-tolerated but may be associated with vascular toxicities such as hemorrhage and hypertensive events, both of which appear to be related to the mechanism of action of these anti-angiogenic agents [19,48,49*].

The need to redefine the therapeutic window for anti-VEGF intervention has become increasingly apparent, as VEGF and VEGF-Rs are required in the adult for the maintenance and function of kidney glomeruli, ovarian corpus luteum angiogenesis, endochondral bone formation, maintenance of alveolar structures, motor neurons of the spinal cord and central nervous system, as well as for hematopoietic stem cells [17**,19,50**]. Nevertheless, the clinical efficacy with bevacizumab (Avastin™, rhuMab-VEGF; Genentech Inc., San Francisco, CA, USA), a mAb targeting VEGF, is encouraging, although hypertension was the most serious adverse event related to this antibody therapy [49*]. Furthermore, the combination of bevacizumab with 5-fluorouracil/leucovorin chemotherapy in metastatic colorectal cancer indicated a trend towards improved survival for patients with unfavorable prognostic indicators [51*]. Similarly, the combination of bevacizumab with carboplatin/paclitaxel in lung cancer patients showed a treatment benefit, although six patients experienced life-threatening episodes of pulmonary hemorrhage [52*]. Nonetheless, retrospective analysis of the trial revealed a significant increase in time for disease progression in the combination arm for patients with advanced non-squamous lung cancer [52*].

In contrast, the clinical efficacy of PTK-directed small-molecule inhibitors targeting the VEGF-R is so far disappointing and is possibly related to the fact that these are first-generation agents. The most advanced VEGF-R PTK inhibitor is, semaxanib (SU5416; Sugen, A Pharmacia Company, San Francisco, CA, USA), which has shown no survival advantage in combination with 5-fluorouracil/leucovorin therapy in a phase III randomized trial, according to the interim analysis [53,54]. As the second generation of these PTK inhibitors directed at VEGF receptors appear to be more selective, less toxic and more potent in murine models of cancer, there is hope of better clinical efficacy. It also seems unlikely that specific agents that block the VEGF or EGF-R/HER-2 signaling pathways will be suitable for monotherapy of solid tumors. However, for non-cancer indications where it might be sufficient to diminish VEGF-upregulated angiogenesis, the anti-angiogenic monotherapy with inhibitors of VEGF signaling might be sufficient treatment.

In summary, it is unclear whether the clinical success obtained with imatinib may be easily extended to other PTK inhibitors for the treatment of solid tumors, even though reasonable preclinical and clinical evidence is available, indicating that increased PTK activity is involved in the pathophysiology of these human malignancies.

Conclusions

Pharmacodynamic endpoints

The clinical efficacy of imatinib has clearly demonstrated the potential of kinase inhibitors. The discovery of imatinib has also shown that the successful development of PTK inhibitors is based primarily on predictive preclinical model systems and on a solid epidemiological association between the targeted kinase or pathway and the disease state; the latter being inevitably associated with large retrospective and/or prospective clinical studies. Thus, the treatment of solid tumors with PTK inhibitors can only be optimized if appropriate pharmacodynamic or biological endpoints and dose regimens are incorporated into clinical trials. Although much emphasis is being placed on biological endpoints in solid tumors, the difficulty in gaining access to solid tumor tissue during clinical trials and the lack of robust and sensitive analytical methodologies have made it extremely difficult to reliably analyze the cellular pathways in tumors or in the normal tissue of the same patients in a non-invasive manner. In this respect, the recent development in the phosphoproteomic area may open new avenues, as these efforts may pave the way to the design of smarter and shorter clinical trials with defined pharmacodynamic endpoints.

Animal models of cancer

To facilitate drug testing, there is also a need for better animal models that allow a more rapid read-out of tumor growth inhibition, and that better reflect the mutations and the molecular pathogenesis of human malignancies. Most of the *in vivo* animal models for cancer suffer from poor predictability [55]. Animal models based on conditional transgene expression and/or conditional gene knockouts are being elaborated upon and may provide more realistic models for solid tumors [56–58] and leukemias [59*,60*]. Furthermore, technologies are being developed that will allow rapid and non-invasive monitoring of tumor growth, as well as imaging of the inhibition of targeted PTK under treatment [61**,62**]. In addition, preclinical model systems (molecular, cellular and *in vivo* animal models) need to be in place to better understand the resistance mechanisms that will inevitably ensue with the use of PTK inhibitors, as treatment with imatinib has demonstrated [37*,38*,39**,40*,41*].

Future prospects

Finally, the selection of epidemiologically relevant, drugable protein kinase targets, coupled to efficient lead finding and optimization of the lead molecule for potency, selectivity, efficacy and biopharmaceutical properties will be key. The recent completion of the human kinome

coupled to expression arrays, phosphoproteomics and substrate recognition databases should provide a catalogue of protein kinases (and phosphatases) and lead to a better understanding of cellular signaling associated with disease. This, in turn, should form the basis for generating targeted PTK inhibitors with the efficacy and tolerability of imatinib.

All these approaches may eventually lead to tailor-made personalized therapeutics that target specific disease conditions. Personalized treatment modalities have the advantage that they are most likely to offer the maximal benefit for the cancer patient both in terms of disease-free survival as well as quality of life. On one hand, these treatment modalities may also inevitably result in an explosion of healthcare costs due to sophisticated diagnostics and patient monitoring that will eventually lead to an increased fragmentation of the cancer market. On the other hand, however, the success story of imatinib is encouraging and has boosted the efforts in the pharmaceutical industry to develop PTK inhibitors with significant benefit for the cancer patient.

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