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Why Imatinib Remains an Exception of Cancer Research

STEVEN D. HORNE,[1] JOSHUA B. STEVENS,[1] BATOUL Y. ABDALLAH,[1] GUO LIU,[1] STEVEN W. BREMER,[1] CHRISTINE J. YE,[2,3] AND HENRY H.Q. HENG[1,3,4]*

[1]*Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, Michigan*

[2]*Department of Internal Medicine, Wayne State University School of Medicine, Detroit, Michigan*

[3]*Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan*

[4]*Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan*

The archetype driving the drug targeting approach to cancer therapy is the success of imatinib against chronic phase chronic myeloid leukemia (CML-CP). Molecular targeting success of this magnitude has yet to be repeated for most solid tumors. To answer why imatinib remains an exception of cancer research, we summarize key features and patterns of evolution that contrast CML-CP from prostate cancer, an example of a solid tumor that also shares a signature fusion gene. Distinctive properties of CML-CP include: a large cell population size that is not geographically constrained, a highly penetrant dominant oncogene that sweeps the entire cell population, subsequent progressive and ordered clonal genetic changes, and the effectiveness of molecular targeting within the chronic phase, which is comparable to the benign phase of solid tumors. CML-CP progression resembles a clonal, stepwise model of evolution, whereas the pattern of solid tumor evolution is highly dynamic and stochastic. The distinguishing features and evolutionary pattern of CML-CP support why the success of imatinib does not carry over to most solid tumors. Changing the focus of cancer research from a gene-based view to a genome-based theory will provide insight into solid tumor evolutionary dynamics.

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Chronic myeloid leukemia (CML) is a hematological disorder characterized by uncontrolled proliferation of cells of the myeloid lineage. CML progresses through three successive stages. Chronic phase chronic myeloid leukemia (CML-CP) can last for years, which continues through an accelerated phase en route to a blast crisis, resembling acute myeloid leukemia or lymphoid leukemia. Within the blast crisis stage, the patient survival time is under a year (Assouline and Lipton, 2011).

The Philadelphia chromosome (Ph) was discovered in 1960 followed by its detailed cytogenetic characterization in 1973 (Nowell and Hungerford, 1960; Rowley, 1973). Translocation of chromosomes 9 and 22 results in the de novo formation of the BCR-ABL fusion oncogene, a constitutively active form of the ABL tyrosine kinase. BCR-ABL kinase hyperactivity enhances proliferation and growth-factor independence while reducing apoptosis (Jabbour et al., 2010; Zhang and Rowley, 2011). The molecular characterization of CML provided rationale for studying all cancer at the gene level and has influenced the entire field.

The mutant BCR-ABL kinase represents a specific cancer target not shared with normal somatic cells, and it was reasoned that, if this specific cancer gene could be targeted, the cancer could be cured. In an effort to inhibit the activity of the BCR-ABL kinase, a small-molecule compound now referred to as imatinib was developed (Druker et al., 1996, 2001). Imatinib blocks the ATP-binding site of BCR-ABL, suppressing kinase signaling and inducing cell death. The results of imatinib therapy are impressive for CML-CP patients, with a 7-year overall survival rate of 86% (Jabbour et al., 2010). Imatinib is currently the recommended first-line therapeutic for CML-CP patients and is accepted as the standard of care.

The overwhelming, inspiring success of imatinib has become the example to follow for cancer research, providing the key rationale in favor of various cancer genome sequencing projects. Vast investments in high-throughput genome sequencing technologies and microarray analyses have resulted in the identification of many candidate molecular targets. Unfortunately, molecular targeting success of this magnitude has yet to be repeated for the majority of solid tumors (Heng et al., 2010b). Identifying recurrent chromosomal changes has proven to be extremely challenging in solid tumors due to the lack of recurrent patterns in most tumor types coupled with a high level of non-clonal chromosome aberrations (NCCAs) and karyotypic heterogeneity (Heppner and Miller, 1998; Albertson et al., 2003; Heng et al., 2004, 2013). The vast majority of gene mutations are not shared among patients, and overwhelming mutational heterogeneity can occur within a tumor (Bielas et al., 2006; Heng, 2007; Ye et al., 2007; Navin et al., 2011). Furthermore, even when a recurrent mutation is present, as in the case of BRAF mutations in melanoma, the effect of a targeted drug such as vemurafenib is dramatic but transient, as tumors invariably become resistant to these agents (Wagle et al., 2011). To understand why the high success of molecular targeting against CML-CP has been difficult to duplicate for most solid tumors, we analyze the following issues.

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*Correspondence to: Henry H.Q. Heng, 3226 Scott Hall, 540 E. Canfield, Detroit, MI 48201. E-mail: hheng@med.wayne.edu

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BOX 1. Select Terminology and Definitions

Term	Definition
Genome	The entity that contains an organism's hereditary information (system inheritance), represented by both gene context and genomic topology The topology of the genome provides the physical basis of genomic architecture and a provides the physical basis of genomic architecture and multi-dimensional interactive relationship that exists between all genes and non-coding sequences The genome is the main evolutionary selection platform
Punctuated phase	Phase of NCCA/CCA cycle that is marked by genome replacement coupled with elevated non-clonal chromosome aberrations
Stepwise phase	Phase of NCCA/CCA cycle that is marked by clonal evolution with clonal chromosome aberrations, where stepwise Darwinian evolution is dominant
NCCA/CCA cycle	Highly dynamic and stochastic pattern of solid tumor evolution Consists of a punctuated phase and a stepwise phase Shifts between phases are induced by stress and subsequent selection Progression during the punctuated phase cannot be traced, unlike in the stepwise phase

Comparative Analyses

Contrasting patterns of evolution

Cancer represents an evolutionary process, where the pattern has been demonstrated to be highly dynamic and stochastic (Merlo et al., 2006; Gatenby et al., 2009b, 2010; Gillies et al., 2012). In particular, solid tumor evolution is cyclical and consists of two distinct phases: a punctuated phase (marked by genome replacement coupled with elevated NCCAs) and a stepwise phase (marked by clonal evolution with dominant clonal chromosome aberrations or CCAs) (Heng et al., 2006a,c, 2011a,b; Heng, 2007, 2013) (Box 1). Shifts between phases are induced by stress and subsequent selection. Recently, this discontinuous pattern of evolution has been supported using single-cell sequencing. At the DNA-level, tumors grow by "punctuated clonal expansion with few persistent intermediates" (Navin et al., 2011). Even if the stepwise phase is detected at the DNA level (which represents the building materials within the genome network), the punctuated phase may persist at the genome level (which represents network architecture), as the same building materials can be utilized to build different structures. Therefore, the key to monitoring cancer evolution is at the genome level rather than the gene level (Heng et al., 2011a).

Discovery of the two phases of cancer evolution is of clinical significance, as specific molecular targeting is most effective within the stepwise phase of evolution, but less useful in the punctuated phase where there are no fixed targets. During the punctuated phase, the genetic landscape of a tumor can drastically and rapidly change, and alterations of the genome network can severely impact drug efficacy.

Based on the key clinical characteristics of CML, its evolutionary pattern resembles the stepwise model of evolution. In fact, the clonal evolution hypothesis is supported by the case of CML and has formed the conceptual framework for current cancer research (Nowell, 1976). Failure of this applied model in tumors has been a continuous source of frustration, especially since solid tumors represent 90% of all malignancies.

The evolutionary process of solid tumors does not fit the gradual linear pattern observed in CML. Most solid tumors are marked by the universal existence of genome heterogeneity, where tumors of the same type often contain unique karyotypes and mutations found within subclones (Heppner and Miller, 1998; Heng et al., 2004, 2006a; Losi et al., 2005; Merlo et al., 2006). High-throughput sequencing has recently confirmed this (Gerlinger et al., 2012). Therefore, it is necessary to illustrate the contrasting patterns between clonal evolution (CML) and stochastic evolution (most solid tumors), which represent the basis behind the failure of applying the targeting success of CML-CP to most solid tumors.

It is important to illustrate why CML and other solid tumors display different patterns of somatic cell evolution. Reviewing the system features and behaviors of CML-CP and prostate cancer reveals the following three key evolutionary characteristics that contrast CML from most solid tumors: fusion gene dominance, temporal order of karyotypic evolution, and causation of cancer progression by a highly penetrant fusion gene. Prostate cancer represents an example of a solid cancer that is the focus of extensive fusion gene research (Tomlins et al., 2005, 2008; Rajput et al., 2007; Tu et al., 2007; Rubin et al., 2011). In particular, the identification of the fusion gene TMPRSS2-ERG in prostate cancer samples has reinforced the hope that a molecular Achilles' heel exists within every cancer.

Fusion gene dominance

CML is characterized by the high-penetrance of the BCR-ABL fusion gene. In most instances, the typical t(9;22) is the sole chromosomal aberration during chronic phase (Johansson et al., 2002). Prostate cancer cases, however, are marked by high karyotypic heterogeneity, and specific single fusion genes occur in reduced frequencies within the patient population. Dozens of chromosomal abnormalities and fusion genes have been identified in prostate cancer cases (Gu and Brothman, 2011), suggesting the involvement of large cohorts of genes and chromosomal aberrations. This is in contrast to the single fusion gene culprit characteristic of CML-CP. A recent study demonstrated the presence of the extensively studied fusion gene TMPRSS2-ERG in only 46% of prostate cancer biopsies (Mosquera et al., 2009). In fact, after comparing published data (28 studies totaling 2,786 patient samples, detailed analysis not shown), the range of TMPRSS2-ERG fusion gene occurrence in prostate cancer patient samples is approximately 15.3–77.8%, with a mathematical average of 42.3%. This suggests that even though fusion genes may be involved in solid tumor progression, the penetrance of the gene products is very different from the high frequency found in CML-CP. It is important to note that, despite the application of large-scale genome sequencing, commonly shared fusion genes have not been identified for most solid tumors.

Temporal order of karyotypic evolution

Despite the high level of additional chromosomal changes detected from the majority of CML patients in blast crisis, along with variance in the temporal order of secondary changes, the preferred pathway appears to start with i(17q), followed by +8 and +Ph, and then +19, suggesting a stepwise pattern of karyotypic evolution from chronic phase to blast crisis (Johansson et al., 2002). Corresponding to the karyotypic changes, the over-expression of the BCR-ABL fusion gene, up-regulation of the EV11 gene, increased telomerase activity, and mutation of RB1, TP53, and CDKN2A have been documented.

A distinct common order of karyotypic evolution has not been characterized in prostate cancer. In contrast, the genomic rearrangements studied in prostate cancer do not occur in a predictable fashion. In a recent paired-end, massively parallel sequencing project of seven prostate cancer patients (Berger et al., 2011), three of the seven tumor samples sequenced were positive for TMPRSS2-ERG rearrangements. Interestingly, but not surprisingly, the sequencing results suggested that TMPRSS2-ERG rearrangement positivity of each sample was

the result of a unique pattern of complex chromosome breakage and rejoining. This supports the discontinuous pattern of solid tumor evolution (Heng et al., 2006a, 2010a), and one would expect a large number of possible chromosomal rearrangement patterns that result in TMPRSS2-ERG rearrangement-positivity.

Causation of cancer progression by a highly penetrant fusion gene

The hyperactivity of the BCR-ABL kinase has been deemed the force driving cells from chronic phase to blast crisis due to its involvement in enhanced proliferation, growth-factor independence, reduced adhesion of tumor cells, and reduced apoptosis. This is supported in mice transgenic for a BCR-ABL p190 DNA construct (Heisterkamp et al., 1990). Of the 10 transgenic mice generated, 8 died or were moribund with acute or chronic leukemia, myeloid or lymphoblastic, between 10 and 58 days after birth. Two of these were diagnosed in the blast crisis of CML. In prostate cancer, however, fusion genes have not been demonstrated as the driving force of disease progression in vivo. Transgenic overexpression of ERG in mice resulted in the development of prostatic intraepithelial neoplasia, but these lesions did not progress to invasive prostate cancer (Klezovitch et al., 2008; Tomlins et al., 2008).

Population structure of hematologic and solid cancers

A review of population genetics further contrasts hematologic and solid cancers (Table I). Population size plays an important role in shaping the evolutionary patterns. Cell populations of hematological malignancies occupy a large blood environment. Within this system, initially altered cells can freely move. Any dominant alteration, such as the appearance of fusion gene products, would have a significant impact on the entire system. According to population genetics, clonal events within a large population can be dominant over non-clonal events (Gerrish and Lenski, 1998). In contrast, altered cells in solid tissues are constrained by tissue geography and local micro-environments are different, unlike the tightly regulated, relatively uniform blood environment. These altered cells represent typical small, isolated populations.

Small population size implies that genetic drift has a greater influence on evolution. Solid tumors, which represent isolated small populations, mediate their evolution through the NCCA/CCA cycle (Heng et al., 2006a). NCCAs develop into different CCAs in different tumors due to the influence of genetic drift. This principle has also been discussed in regard to the correlation between dominant mutation types, the size of a tissue within a cellular compartment, and the size of a stem cell pool (Frank and Nowak, 2004). Tissue compartments with large stem cell pools often incur rapid cellular proliferation caused by tumor suppressor and oncogene mutation, whereas small stem cell pools may often initiate cancer progression via genetic instability (Frank and Nowak, 2004). A direct link between NCCAs and genomic instability was found after observing elevated frequencies of NCCAs of various cell lines and animal models carrying defects in genes responsible for maintaining genetic diversity (Heng et al., 2006b,c, 2009, 2011a). On the other hand, CCAs are associated with dominant pathways, which explains the dominance of fusion genes in the large population blood cancers and the heterogeneity of aberrations detected from the small and isolated population solid tumors. As a result, the evolutionary process of these different isolated populations is diverse, requiring a longer time to evolve due to additional system constraint.

Comparing different stages of disease progression

As CML patients progress from the chronic phase into the accelerated and blast crisis stages, imatinib efficacy plummets. Complete cytogenetic response in early chronic phase patients placed on imatinib is approximately 80%. This falls to ~8% in blast crisis (Radich, 2007), where the median survival time is measured in months (Assouline and Lipton, 2011). This compares to the efficacy of EGFR targeting in prostate cancer, as monotherapy agents have failed to demonstrate high antitumor activity in clinical trials (Canil et al., 2005; Gravis et al., 2008; Guérin et al., 2010; Sridhar et al., 2010).

The frequency of additional chromosomal abnormalities increases with progression in CML. This frequency is ~7% in chronic phase patients and jumps to 40–70% in the advanced stages (Skorski, 2011). These advanced stages of the disease resemble the majority of solid tumors, where the increase of genomic instability and accumulation of genetic changes are key features that are age-related and are responsible for a relatively longer time period for the cancer to develop and progress. The linkage between genomic instability and poor prognosis has been well documented in both hematologic and solid cancer patients (Nishizaki et al., 2002; Nakamura et al., 2003; Caraway et al., 2008; Sato et al., 2010; Zamecnikova et al., 2010).

We then suggest that with imatinib, we are actually treating a stage of CML that is comparable to the benign phase of solid tumors. Unfortunately, while a dominant CML-CP signature (BCR-ABL) has been identified with cytogenetic techniques, a dominant specific fusion gene that drives cancer progression has yet to be identified in prostatic benign tissue. If a dominant fusion gene was present in benign tissue that acted as a driving force in the progression of solid tumors, clinicians could identify threatening tissues before they became problematic. Similar to the elimination of chronic phase leukemic cells with imatinib, extraction of these threatening benign tissues conceptually would be much more effective than current treatments on late-stage solid tumors. Unfortunately, this is clearly not the case in prostate cancer progression.

TABLE I. Evolutionary characteristics of hematologic and solid cancers

Feature	Hematological malignancies	Solid cancers
Cell population size	Large population size	Small population size
Cell motility	Cells are free to migrate throughout blood environment	Cells populations are isolated and constrained by tissue geography
Genetic drift	Lower influence on large populations	Greater influence on small populations
Micro-environment	Blood stream is tightly regulated and relatively uniform (glucose and oxygen levels, pH, etc.)	Micro-environments vary widely within and between tissues
Cell metabolism	Influenced by normoxic conditions, regulated nutritional levels	Varies depending on normoxic/hypoxic conditions and nutritional gradients
Drug delivery/targeting efficiency	Free motility of cells allows for optimal drug targeting	Varying environments may affect drug chemistry, stationary tumor masses of cells potentially hinder drug targeting and penetration
Cell lineage of disease onset	Early lineage displays more defined differentiation and is characterized by orderly and more predictable stages	Late lineage displays less linear progression and is characterized by stochastic, unpredictable stages

Conclusions

Molecular targeting success is, unfortunately, very limited in other cancer types where the evolutionary patterns are significantly different. While CML-CP clearly represents a stepwise model, most detectable solid tumors likely have undergone multiple rounds of the two-phase cycle of evolution. The associated genome dynamics make it very difficult to successfully apply molecular targeting approaches against most solid tumors. Furthermore, if one particular pathway of a solid tumor is blocked by a specific therapy, genomic instability can relieve the requirement for that pathway within the population of surviving cells. This is evidenced by the demonstration that drug treatment can induce the recently introduced phenomenon of genome chaos, where major genome reorganization is achieved in a short period of time following chromosome fragmentation (Heng et al., 2006c, 2011b; Stevens et al., 2007, 2011a). This view is in agreement with the clinical observations that CML responds to imatinib more effectively during the chronic phase than during blast crisis where new karyotypic aberrations are detectable.

Despite attempts to apply molecular targeting principles to solid tumors, clinical outcomes have been far from ideal. Metastatic melanoma patients treated with vemurafenib (targeting the BRAF V600E mutation) for 6 months had a 20% overall survival increase compared to dacarbazine treatment (Chapman et al., 2011). However, between the 9- and 10-month mark, the overall survival trends of these two treatments appear to converge, suggesting that vemurafenib may prolong the survival of metastatic melanoma patients by approximately 2 months. A 4-year study regarding trastuzumab as part of an adjuvant treatment regimen against HER2-positive breast cancer concluded that patients treated with trastuzumab for 1 year had an overall survival increase of 1.6% over those observed without treatment (Gianni et al., 2011). Such cases do not mimic the overwhelming success of imatinib.

Studies of 82 non-small-cell lung cancer (NSCLC) patients treated with crizotinib targeting the EML4-ALK fusion gene observed 1- and 2-year overall survival rates of 74% and 54%, compared to 1- and 2-year overall survival rates of 72% and 36% of ALK-positive crizotinib-naïve control patients (Kwak et al., 2010; Shaw et al., 2011). Based on previous data from targeted therapy trials of other solid tumors, one would expect further decline in survival as this study continues. A recent meta-analysis of 13 randomized trials evaluating the effects of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (erlotinib and gefitinib) in 1,260 patients with EGFR-mutated NSCLCs concluded that despite a higher response rate than platinum-based chemotherapy (67.6% vs. 32.8%, respectively), EGFR tyrosine kinase inhibitors do not significantly improve the overall survival of patients compared to control groups (hazard ratio = 0.96; Petrelli et al., 2012). These studies indicate, unfortunately, that the molecular targeting success against CML-CP has not been replicated in the clinic against most solid tumors.

Interestingly, treating PML-RARA-positive acute promyelocytic leukemia (APL) patients with a combination of arsenic trioxide and all-trans retinoic acid has been very successful, with a 5-year overall survival rate of 97.4% (Hu et al., 2009). This is not surprising considering the parallels between APL and CML-CP where both are typically characterized by a highly penetrant, dominant fusion gene (PML-RARA is found in over 98% of APL cases) (Vitoux et al., 2007). In contrast, the fusion gene EML4-ALK is found in only 4% of NSCLC cases (Shaw et al., 2011). Like BCR-ABL mouse models, PML-RARA expression yields APL in transgenic mice (de The and Chen, 2010), demonstrating the direct link between the fusion gene and the onset of the disease. Both diseases are hematological malignancies with similar population structures, ultimately allowing for a dominant alteration (e.g. fusion gene) to have a significant impact on the entire system. It is therefore likely that some subtypes of cancer could be effectively treated using target-specific or even less specific therapy, during the stepwise phase of cancer evolution, when they have evolutionary patterns similar to those of CML and APL. Of course, molecular targeting can further reduce potential side effects otherwise associated with harsh, general cellular mechanism-focused treatment such as chemotherapy.

The application of fusion genes in the diagnosis of solid tumors also has limited implications due to the inaccessibility of threatening benign tissues using current sampling techniques. A simple, accurate, and informative blood draw can be performed to diagnose patients with BCR-ABL positive chronic phase leukemia due to the constant circulation of leukemic cells in the blood stream. However, fusion gene identification in threatening benign tissue within an asymptomatic individual is problematic. Current biopsies collect only a small sample of suspect tissue. Even if the sample contains altered tissue, the biopsy will not likely indicate the complete genomic profile of the tumor, given the vast genomic heterogeneity associated with solid tumors. This is unfortunate because if we could identify solid tumors in the benign phase, for many cases, surgical resection would be sufficient even without drug treatment.

This comparison also sheds light on the concept of oncogene addiction, where tumor maintenance is dependent on the constitutive activity of oncogenes, and inhibition of this activity leads to tumor cell death, differentiation, arrest, or senescence (Luo et al., 2009). This concept is supported by a BCR-ABL1-tetracycline transactivator double transgenic mouse study (Huettner et al., 2000). Reversion of the leukemic phenotype and complete remission were achieved after suppression of the BCR-ABL1 gene. However, this concept fails to extend to most types of cancer due to the lack of a dominant gene product that drives cancer progression in early lineages. In addition, any oncogene addiction can be lost to subsequent rounds of the NCCA/CCA cycle, resulting in system-wide changes that can impact target-specific drug resistance without necessarily resulting in additional mutations to the target gene product. This explains the loss of oncogene addiction seen in lung cancer, breast cancer, as well as the blast crisis of CML, despite the expression of targetable EGFR, HER2, and BCR-ABL, respectively (Hochhaus et al., 2002; Sharma et al., 2007; Valabrega et al., 2007). We can confirm that under only very rare, special circumstances does this model of oncogene addiction actually apply to cancer.

Imatinib-resistant CML cases have been attributed to point mutations in the BCR-ABL gene, however, these mutations are actually found in only a small subset of imatinib-resistant BCR-ABL CML cases (Deininger et al., 2005). A recent study of the apoptotic machinery of BCR-ABL-driven leukemia suggested that the complexity of the disease clearly extends beyond any point mutations that may occur within the kinase as cases with higher resistance actually involve additional genomic changes rather than new kinase point mutations (Kaufmann, 2006). Our recent study of cell death heterogeneity may explain this problem. Since the cell death process can also favor cancer evolution by changing multiple levels of genetic and epigenetic organization, there are many off-target and adverse effects (Stevens et al., 2013). Extension of the fusion gene target model derived from CML-CP to solid tumors will be ineffective due to the even greater complexity and heterogeneity within these diseases, therefore, we can no longer follow CML's lead in the design of future cancer research.

What is the new direction we should take in the war against cancer, since specific molecular targeting has not been an ideal approach for most solid tumor types due to overwhelming genome instability in most solid tumors? A new, promising

strategy involves treating cancer progression as system evolution, where focusing on the overall pattern of system evolution rather than targeting individual genes may provide the answer (Heng et al., 2006a,b,c, 2010a, 2011a; Gatenby et al., 2009a,b, 2010; Gillies et al., 2012). One established system of using NCCAs to study karyotypic heterogeneity and monitor the speed and phases of cancer evolution represents such an example (Heng et al., 2009; Ye et al., 2009; Stevens et al., 2011b; Heng, 2012). The key here is to constrain the speed of tumor growth without triggering genome chaos, which promotes the emergence of aggressive, drug-resistant tumor subpopulations. Targeting specific pathways works well only when the system is stable, during the stepwise phase, however, for unstable systems, pathway targeting is quickly overcome by the evolution of the system. Even worse, through genome chaos, new pathways are selected and constructed, and new genomes (systems) are rapidly formed. Therefore, drug intervention can, in fact, paradoxically promote cancer evolution when applied in the wrong phase (Maley et al., 2004). In contrast, slowing the evolutionary process by carefully constraining the system without promoting genome chaos will improve patient prognosis (Heng, 2013).

The main purpose of our analysis is not just to be critical of current efforts, nor to offer precise solutions, but to call upon investigators to actively discuss this important issue, which is crucial for our future efforts towards winning the war on cancer. Such action is urgently needed, as there are currently two opposite viewpoints when dealing with this question. On one side, is that it is well known that imatinib represents an exception, but without a clear explanation. Paradoxically, other researchers believe that, with continued efforts, the success of imatinib in CML-CP will be duplicated in most solid tumors. With this evolutionary analysis, we hope that we have done the first key step by challenging the research community to face this reality and adopt a new understanding of cancer. With the correct conceptual framework, we can make the next triumph of cancer research (Heng, 2007, 2012, 2013; Heng et al., 2011a,b).

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