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Reproductive fitness advantage of *BCR–ABL* expressing leukemia cells

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ABSTRACT

Mutations in oncogenes and tumor suppressor genes confer a fitness advantage to cells that can lead to cancer. The tumor phenotype normally results from the interaction of many mutant genes making it difficult to estimate the fitness advantage provided by any oncogene, except when tumors depend on one oncogene only. We utilize a model of chronic myeloid leukemia (CML), to quantitate the fitness advantage conferred by expression of *BCR–ABL* in hematopoietic cells from *in vivo* patient data. We show that *BCR–ABL* expression provides a high fitness advantage, which explains why this single mutation drives the chronic phase of CML.

1. Introduction

Cancer development is due to the serial accumulation of mutations in oncogenes and tumor suppressor genes [1,2]. These mutations often enable cells to replicate autonomously, become less dependent on external growth control stimuli, or fail to undergo apoptosis [1]. Cancer is a process of somatic evolution, where oncogenic mutations provide a fitness advantage to a cell population, enabling clonal expansion [3–5]. Experimental quantification of the actual fitness advantage conferred by such mutations is difficult for several reasons. Often mutations in several genes are necessary to establish the cancer phenotype making it difficult to infer the impact of each mutation on reproductive fitness [2,6]. Moreover, it is difficult to reproduce the *in vivo* microenvironment that defines the fitness of mutant versus normal cells. In this regard, chronic myeloid leukemia (CML) provides a paradigmatic example, because it requires a single mutation to develop.

Various studies suggest that chronic phase CML can be explained by the expression of *BCR–ABL* in hematopoietic cells [7,8], enhancing their self-renewal capacity [9–11]. Recently, we have developed a model of CML which provides a unified view of disease development, response to imatinib therapy and relapse [12]. Using this model, we were able to quantitate the enhanced self-renewal of CML progenitor cells. In the following, we extend this model to derive a relationship between a change in the self-renewal probability of CML cells and reproductive fitness, enabling us to determine the fitness advantage provided by the *BCR–ABL* oncogene to cells. We illustrate how imatinib therapy reverses the fitness advantage conferred by *BCR–ABL*, explaining the response to therapy.

2. Materials and methods

2.1. In vivo dynamics and parameter estimation

Hematopoiesis can be described as a hierarchical multi-compartmental process where N_k cells in a given compartment k replicate at a rate r_k (for details, cf. Ref. [13] and Fig. 1). With probability ε, both daughter cells produced

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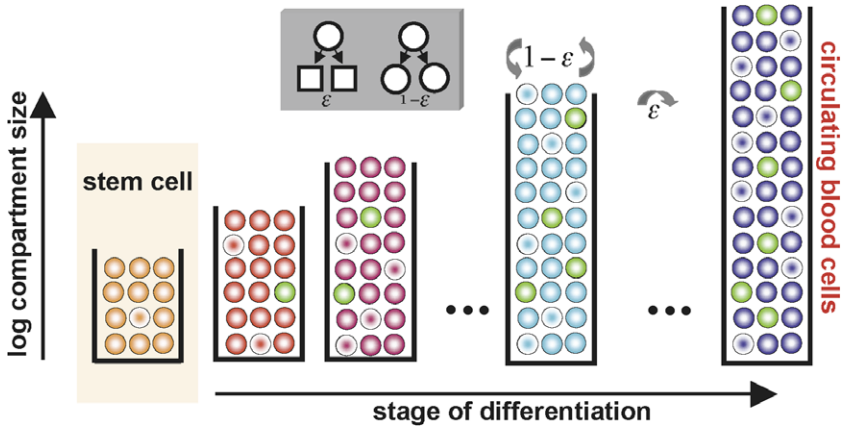

Fig. 1. A hierarchical, multicompartment model of hematopoiesis under normal conditions and in CML. Except of at the stem cell level, when a cell divides, with probability ε_0, the daughter cells differentiate and migrate to the next downstream compartment but with probability $1 - \varepsilon_0$, the cell undergoes self-renewal and both cells remain in the same compartment. Cells lost from one compartment due to differentiation are replaced by cells from the next upstream compartment. The stem cells divide asymmetrically to maintain all downstream compartments functional. The appearance of the CML stem cell starts the process leading to disease. CML cells downstream of the stem cell pool have a higher probability of self-renewal: $\varepsilon_{CML} < \varepsilon$ enabling them to dominate hematopoiesis. Therapy with imatinib only affects a fraction of CML cells and alters their self-renewal capability: $\varepsilon_{CML} < \varepsilon_0 < \varepsilon_{IMAT}$.

via mitosis differentiate and migrate to the next downstream compartment $k + 1$. With probability $1 - \varepsilon$, the cell self-renews and both daughter cells remain in compartment k. Loss of cells from compartment k (differentiation) is compensated by influx of cells from compartment $k - 1$, so that all compartments are coupled. Normal hematopoiesis corresponds to steady state conditions. Using quantitative data on granulopoiesis that combines morphology and isotope labeling of cells [14–16], we estimated that $\varepsilon_0 = 0.85$ across all compartments downstream of hematopoietic stem cells (Fig. 1) [13]. In the absence of experimental data to the contrary, the model considers that cell behavior across hematopoiesis is constant. Despite this assumption, the model is able to accurately predict clone size and lifetime of *PIG-A* mutant populations in healthy subjects as determined by an independent group of investigators [17]. The model also predicts the number of divisions that link hematopoietic stem cells with circulating blood cells [18,19] suggesting that the model assumptions and parameters obtained for normal hematopoiesis are reliable. Although the model does not explicitly consider the possibility of asymmetric division at the level of the individual cell, it accommodates this feature at a population level (since this in essence, is a cell population phenomenon [20,21]). A detailed analysis of the impact of asymmetric cell division on mutant clone dynamics has been reported elsewhere [22].

In CML, hematopoiesis is disturbed because expression of *BCR–ABL* enhances self-renewal of the mutated *progenitor* cells [9–11]. The result is bone marrow expansion [23] and increased hematopoietic output [24]. Therefore, *BCR–ABL* expression alters the self-renewal potential ε of CML cells, while imatinib therapy alters the self-renewal potential of a fraction of the tumor population that are under therapy [10,25]. Importantly, *BCR–ABL* expression does not affect the self-renewal properties of the leukemic stem cell [26], a fact that has considerable implications for disease biology and its therapy [27]. Similarly, in our model, *BCR–ABL* has no impact on the reproductive behavior of terminally differentiated cells since these cells do not reproduce and are insensitive to the effect of imatinib. In order to determine the value of these parameters (ε_{CML} and ε_{IMAT}), we performed a non-linear least squares fit of our mathematical model to data from an international clinical trial where tumor burden was estimated serially by quantitative reverse transcriptase polymerase chain reaction for *BCR–ABL* before and during therapy with imatinib as reported previously [28,29] (Fig. 2). We have fitted the dynamics of the response to imatinib therapy to data reported by Roeder et al. [29] where patients were treated for up to 6 years. Data fitting requires the imposition of certain conditions including: (i) CML starts from one leukemic stem cell (also in Ref. [29]), (ii) the time from the appearance of the first leukemic stem cell to diagnosis is in the range of 5–6 years [30], (iii) diagnosis is associated with an increased hematopoietic output (approximately 3-fold increase compared to normal) [24]. To estimate the error of ε_{CML}, we determined the values of ε_{CML} that alter the time to diagnosis by 25% in either direction. Subsequently, these values were used to determine ε_{IMAT} via a least squares optimization fit, to see how robust the best fit to the extended therapy data reported in Roeder et al. [29] is when ε_{CML} is altered.

2.2. *BCR–ABL* expression and reproductive fitness

Given that the main phenotypic effect of *BCR–ABL* expression is to enhance the self-renewal of CML progenitor cells [10,25], in order to infer the fitness advantage of such an oncogene, we need to translate self-renewal into reproductive success. We start by considering a specific compartment k *downstream* of the stem cell pool (i.e. compartments housing progenitor or more differentiated cells) composed of i CML and $N_k - i$ normal cells. Over short time intervals, the total number of cells remains constant. The

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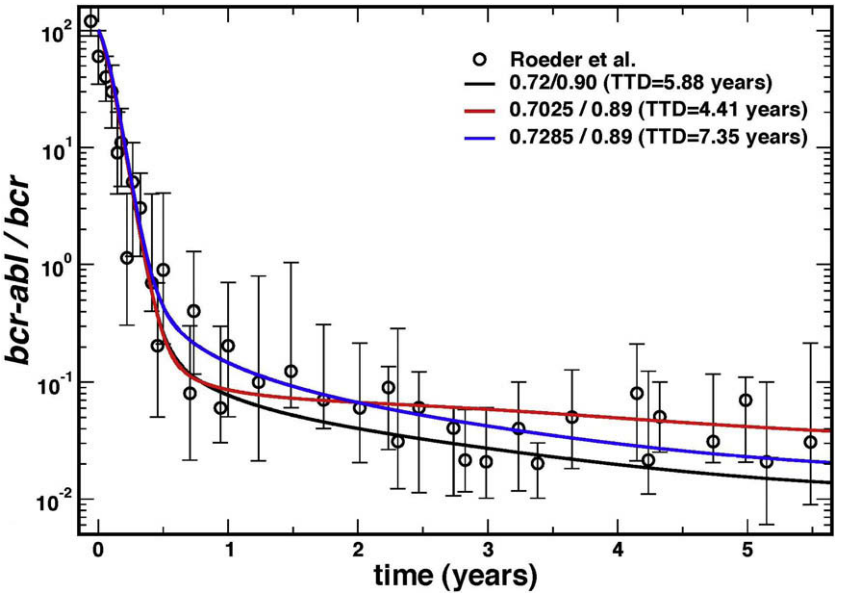

Fig. 2. Dynamics of CML under imatinib therapy. The values for ε_{CML} and ε_{IMAT} were determined using known constraints on CML dynamics, including the time to diagnosis from the appearance of the first leukemic stem cell and the observed responses to imatinib therapy (see Section 2 for details). For each solid line 2 numerical values are provided: the first corresponds to the value used for ε_{CML} whereas the second corresponds to ε_{IMAT}: variation in ε_{CML} was derived letting the Time To Diagnosis (TTD in legend, in years) vary by 25% with respect to the TTD corresponding to the best fit to the data. Subsequently, and for fixed values of ε_{CML}, ε_{IMAT} was determined by optimizing the least squares fit to the data.

probability that the number of CML cells increases due to self-renewal [31] during this time interval is given by

$$T^{+}_{CML}(i) = (1-\varepsilon_{CML})\frac{i}{N_k}. \quad (1)$$

whereas the probability that their number decreases due to differentiation is

$$T^{-}_{CML}(i) = \varepsilon_{CML}\frac{i}{N_k}. \quad (2)$$

The corresponding probabilities for normal cells in the same compartment are

$$T^{+}_{0}(i) = (1-\varepsilon_0)\frac{N_k - i}{N_k}, \quad \text{and} \quad T^{-}_{0}(i) = \varepsilon_0\frac{N_k - i}{N_k}.$$

The ratio ρ of self-renewal to differentiation probability becomes independent of N_k and i:

$$\rho_{CML} = \frac{T^{+}_{CML}(i)}{T^{-}_{CML}(i)} = \frac{1-\varepsilon_{CML}}{\varepsilon_{CML}} \quad \text{while} \quad \rho_0 = \frac{1-\varepsilon_0}{\varepsilon_0}.$$

The quantity ρ provides a measure of fitness and since self-renewal is less likely than differentiation ($\varepsilon_0 > 0.5$) [13] we have $\rho_0 < 1$. This is caused by the hierarchical population structure: in a standard Moran model of evolutionary dynamics, the baseline value for ρ would be 1. Self-renewal of cells implies that they are retained within a compartment for some average number of cell divisions n until the cell differentiates and leaves that compartment. The probability that a cell undergoes t cell divisions in a compartment is given by $(1-\varepsilon)^{t-1}\varepsilon^1$. Thus, n is given by

$$n = \sum_{t=1}^{\infty}(1-\varepsilon)^{t-1}\varepsilon \cdot t = \frac{1}{\varepsilon}. \quad (3)$$

The average number of offspring a particular cell leaves in a compartment before it differentiates is given by $n-1$ (because all cell divisions except the last one produce offspring in a compartment).

Let us define relative reproductive fitness of a cell with differentiation probability ε_j (j standing for normal, CML or IMAT cells) as

$$f_j = \frac{\rho_j}{\rho_0} = \frac{1-\varepsilon_j}{1-\varepsilon_0}\frac{\varepsilon_0}{\varepsilon_j}. \quad (4)$$

Cells with $\varepsilon_j > \varepsilon_0$ will have a relative fitness $f_j > 1$, while $\varepsilon_j < \varepsilon_0$ gives $f_j < 1$. Note that $n - 1 = \rho$, such that we recover the same reproductive fitness measure f_j as above from considering the relative number of offspring in a given compartment. This is compatible with prior work showing that enhanced self-renewal provides a fitness advantage to a cell [22].

3. Results

3.1. Model parameters

The condition $\varepsilon > 0.5$ implies that the number of cells increases exponentially with the degree of differentiation [13] compatible with the generally accepted view of hematopoietic cell dynamics [32–34]. Taking into consideration the constraints described in the Section 2, we fitted the mathematical model to experimental data from Roeder et al. [29]. For an average time to diagnosis of 5.88 years ± 25% (i.e. a time to diagnosis of 4.4–7.4 years), we determined that $\varepsilon_{CML} = 0.72$ (range 0.7025–0.7285) (Fig. 2). Under the same conditions, we estimate that for CML cells

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responding to therapy with imatinib, $\varepsilon_{IMAT} = 0.89–0.90$, that is, we obtain variability values of 3% and 2% in ε_{CML} and ε_{IMAT}, respectively. This illustrates the robustness of our approach.

3.2. BCR–ABL oncogene fitness

Using the above parameter estimates, from Eq. (4), we determined that *BCR–ABL* expression gives CML cells a relative fitness advantage $f_{CML} \approx 2.2$ (2.11–2.4). Note that an error in ε_0 would be reflected as an error in fitness as $\frac{\Delta f}{f} = \frac{1}{1-\varepsilon_0}\frac{\Delta \varepsilon_0}{\varepsilon_0}$. For example, an error of 2% in ε_0 would change fitness by 13%. These values for f_{CML} are considered very large fitness advantages in evolutionary biology. Fig. 3 provides a graphic representation of the fitness ratio as a function of differentiation probability. For imatinib-treated CML cells, Eq. (4) gives $f_{IMAT} \approx 0.70$ (0.63–0.70), a significant fitness disadvantage compared to normal hematopoietic cells (Fig. 3). The benefit of this approach is that fitness does not have to be measured directly, being instead determined by the differentiation probability inferred from disease dynamics.

Using Eq. (3) we can estimate the average number of cell divisions for CML or normal cells in a given hematopoietic compartment. The enhanced self-renewal of CML cells ($\varepsilon_{CML} < \varepsilon_0$) means that they will be retained longer in a given compartment and grow to constitute higher fractions of cells in that and downstream compartments [35]. Consequently, higher fitness does not necessarily mean that disease dynamics is faster [22]. Indeed, it is possible that the disease can take longer to be clinically detectable when fitness is higher, but the clone will be more robust and persistent.

4. Discussion

The development of cancer is perhaps an unavoidable consequence of multicellularity. Health requires that all specialized cells obey rules that regulate their growth [1]. However, mutations are inevitable, giving rise to selective pressure [3–5]. Often mutations are deleterious and the cell dies but some mutations give the cell a fitness advantage and the mutant expands into a clone that can lead to a tumor. Viewed in this way, cancer is an evolutionary process that occurs within an organism. Fundamental to this view is the concept of reproductive fitness, a measure of the advantage that a mutation confers to a cell given the environment. Although some mutations may not directly alter the rate of cellular reproduction, indirectly, the relevant mutations may improve the cell's reproductive potential for example by enabling the cell to survive for longer (anti-apoptotic mutation) or be less dependent on external growth factors (e.g. *JAK2* V617F in hematopoietic cells) [1].

Here, we provided an estimate for the fitness advantage conferred to a cell by an oncogene. This is possible because CML dynamics are well understood due to the presence of a quantifiable molecular marker and the availability of targeted therapy [36]. As a result, one can mathematically model disease dynamics and infer the relative fitness advantage provided by a single oncogene from *in vivo* data [12]. From our analysis, *BCR–ABL* provides a very strong fitness advantage to hematopoietic progenitor cells ($f_{CML} \approx 2.2$ compared to $f_0 \approx 1$). This explains why a single defect can drive clonal expansion in chronic phase CML [7–11]. It is tempting to infer that the fitness advantage provided by many oncogenes and tumor suppressor genes is relatively small, hence the cancer phenotype requires several mutations [2,6]. Perhaps distributing cellular control across many genes that individually make only a small contribution to the cell's fitness, constitutes a successful evolutionary strategy towards reducing the risk of cancer.

The current analysis can only provide an 'average' estimate of the fitness advantage provided by *BCR–ABL* expression in hematopoietic cells. Although the model can accommodate a differential effect of *BCR–ABL* expression on various subpopulations within hematopoiesis, in the absence of reliable data that clearly determines the impact of this oncogene on specific cells, it is difficult to try and perform such an analysis. However, it is important for the reader to realize, that in our model, we do take into consideration the fact that *BCR–ABL* expression does not alter the dynamic properties (self-renewal) of the leukemic stem cells that reside within the first compartment of our model [26,27]. Therefore, the model is compatible with

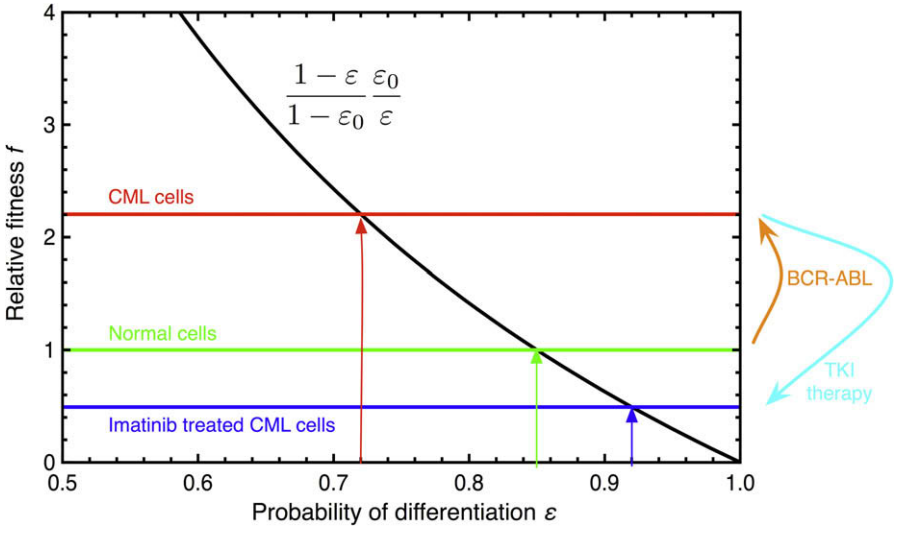

Fig. 3. Relative reproductive fitness due to *BCR–ABL* expression in cells. We estimated the relative fitness of CML cells as a function of self-renewal probability using the estimates of ε_{CML}, ε_0 and ε_{IMAT}. Imatinib reduces the fitness of CML cells to below normal levels, reducing the tumor burden and enabling normal hematopoietic cells to dominate hematopoiesis.

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the current view that CML is a stem cell derived disease but driven by the expansion of progenitor cells such as CFU-GEMM and CFU-GM that reside downstream of the HSC [37]. The lack of a phenotypic effect of *BCR–ABL* on the leukemic stem cell pool has important implications that have been discussed elsewhere [27]. Moreover, in the current model, *BCR–ABL* provides no fitness advantage to terminally differentiated cells and imatinib has no impact on the dynamics of these cells either. Not all patients with chronic phase CML have the same dynamics of response to imatinib [28,29]. This variability has many possible explanations including (i) the intrinsic stochastic dynamics of hematopoietic cell division [20,21], (ii) the probabilistic and reversible inhibition of *BCR–ABL* function by imatinib [25], (iii) variability in intravascular α_1-acid glycoprotein concentration that can trap imatinib in the circulation negating it access to the tumor cell population [38], and (iv) concomitant genetic and epigenetic changes in CML cells that could alter their behavior in unknown ways. These aspects are not taken into consideration by our current model and most probably, the fitness advantage conferred by *BCR–ABL* will be slightly different across patients. Therefore we purposefully do not consider the inter-patient variability in the response to imatinib therapy.

The current analysis illustrates that the definition of a fitness measure in hierarchical structured cell populations is subtler than in unstructured populations. Moreover, it shows that reproductive fitness does not necessarily mean that mutant cells divide at faster rates compared to normal cells within the same tissue. It is important to understand how therapy alters the fitness of mutant cells relative to normal ones. We find that imatinib gives CML cells a significant fitness *disadvantage* compared to normal cells, enabling the latter to regain control of hematopoiesis. To our knowledge, imatinib is the first drug that *selectively* reduces the fitness of cancer cells, leading to excellent disease control. Novel cancer therapeutics should be designed with this in mind – a reduction of the relative reproductive fitness of tumor cells is perhaps more important than actual killing of the malignant clone. In summary, we provide an estimate for the fitness advantage associated with a prototypic oncogene. Our approach illustrates the importance of applying evolutionary concepts to understand cancer biology and its therapy.

Conflict of interest

No author has any conflicts of interest to declare.

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References

[1] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, Cell 100 (2000) 57–70.
[2] B. Vogelstein, K.W. Kinzler, Cancer genes and the pathways they control, Nat. Med. 10 (2004) 789–799.
[3] I. Tomlinson, W. Bodmer, Selection, the mutation rate and cancer: ensuring that the tail does not wag the dog, Nat. Med. 5 (1999) 11–12.
[4] J. Cairns, Mutation selection and the natural history of cancer, Nature 255 (1975) 197–200.
[5] J. Cairns, Mutation and cancer: the antecedents to our studies of adaptive mutation, Genetics 148 (1998) 1433–1440.
[6] N. Beerenwinkel, T. Antal, D. Dingli, A. Traulsen, K.W. Kinzler, V.E. Velculescu, B. Vogelstein, M.A. Nowak, Genetic progression and the waiting time to cancer, PLoS Comput. Biol. 3 (2007) e225.
[7] G.Q. Daley, R.A. Van Etten, D. Baltimore, Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome, Science 247 (1990) 824–830.
[8] R.C. Zhao, Y. Jiang, C.M. Verfaillie, A model of human p210(BCR/ABL)-mediated chronic myelogenous leukemia by transduction of primary normal human CD34(+) cells with a BCR/ABL-containing retroviral vector, Blood 97 (2001) 2406–2412.
[9] S.B. Marley, R.J. Davidson, J.M. Goldman, M.Y. Gordon, Combination of interferon alpha with either Ara-C or ATRA in vitro reduces the selective action of interferon against CML CFU-GM, Leukemia 14 (2000) 1396–1400.
[10] S.B. Marley, R.J. Davidson, J.M. Goldman, M.Y. Gordon, Effects of combinations of therapeutic agents on the proliferation of progenitor cells in chronic myeloid leukaemia, Brit. J. Haematol. 116 (2002) 162–165.
[11] S.B. Marley, J.L. Lewis, J.M. Goldman, M.Y. Gordon, Abnormal kinetics of colony formation by erythroid burst-forming units (BFU-E) in chronic myeloid leukaemia, Brit. J. Haematol. 93 (1996) 878–883.
[12] D. Dingli, A. Traulsen, J.M. Pacheco, Chronic myeloid leukemia: origin, development, response to therapy, and relapse, Clin. Leukemia 2 (2008) 133–139.
[13] D. Dingli, A. Traulsen, J.M. Pacheco, Compartmental architecture and dynamics of hematopoiesis, PLoS ONE 2 (2007) e345.
[14] D.M. Donohue, R.H. Reiff, M.L. Hanson, Y. Betson, C.A. Finch, Quantitative measurement of the erythrocytic and granulocytic cells of the marrow and blood, J. Clin. Invest. 37 (1958) 1571–1576.
[15] E.P. Cronkite, T.M. Fliedner, Granulocytopoiesis, New Engl. J. Med. 270 (1964) 1403–1408. CONCL.
[16] E.P. Cronkite, T.M. Fliedner, Granulocytopoiesis, New Engl. J. Med. 270 (1964) 1347–1352 (CONTD).
[17] D.J. Araten, K. Nafa, K. Pakdeesuwan, L. Luzzatto, Clonal populations of hematopoietic cells with paroxysmal nocturnal hemoglobinuria genotype and phenotype are present in normal individuals, Proc. Natl. Acad. Sci. USA 96 (1999) 5209–5214.
[18] H. Vaziri, W. Dragowska, R.C. Allsopp, T.E. Thomas, C.B. Harley, P.M. Lansdorp, Evidence for a mitotic clock in human hematopoietic stem cells: loss of telomeric DNA with age, Proc. Natl. Acad. Sci. USA 91 (1994) 9857–9860.
[19] N. Rufer, T.H. Brummendorf, S. Kolvraa, C. Bischoff, K. Christensen, L. Wadsworth, M. Schulzer, P.M. Lansdorp, Telomere fluorescence measurements in granulocytes and T lymphocyte subsets point to a high turnover of hematopoietic stem cells and memory T cells in early childhood, J. Exp. Med. 190 (1999) 157–167.
[20] M.Y. Gordon, N.M. Blackett, Routes to repopulation – a unification of the stochastic model and separation of stem-cell subpopulations, Leukemia 8 (1994) 1068–1072 (discussion 1072-3).
[21] J.L. Abkowitz, S.N. Catlin, P. Guttorp, Evidence that hematopoiesis may be a stochastic process in vivo, Nat. Med. 2 (1996) 190–197.
[22] D. Dingli, A. Traulsen, F. Michor, (A) Symmetric stem cell replication and cancer, PLoS Comput. Biol. 3 (2007) e53.
[23] D. Primo, M.L. Sanchez, A.B. Espinosa, M.D. Tabernero, A. Rasillo, J.M. Sayagues, M. Gonzalez, J.M. Hernandez, A. Orfao, Lineage involvement in chronic myeloid leukaemia: comparison between MBCR/ABL and mBCR/ABL cases, Brit. J. Haematol. 132 (2006) 736–739.
[24] T.L. Holyoake, X. Jiang, M.W. Drummond, A.C. Eaves, C.J. Eaves, Elucidating critical mechanisms of deregulated stem cell turnover in the chronic phase of chronic myeloid leukemia, Leukemia 16 (2002) 549–558.
[25] B.J. Druker, S. Tamura, E. Buchdunger, S. Ohno, G.M. Segal, S. Fanning, J. Zimmermann, N.B. Lydon, Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr–Abl positive cells, Nat. Med. 2 (1996) 561–566.
[26] B.J. Huntly, H. Shigematsu, K. Deguchi, B.H. Lee, S. Mizuno, N. Duclos, R. Rowan, S. Amaral, D. Curley, I.R. Williams, K. Akashi, D.G. Gilliland, MOZ-TIF2, but not BCR–ABL, confers properties of leukemic stem cells to committed murine hematopoietic progenitors, Cancer Cell 6 (2004) 587–596.

Please cite this article in press as: A. Traulsen et al., Reproductive fitness advantage of *BCR–ABL* expressing leukemia cells, Cancer Lett. (2010), doi:10.1016/j.canlet.2010.01.020

[27] T. Lenaerts, J.M. Pacheco, A. Traulsen, D. Dingli, Tyrosine kinase inhibitor therapy can cure chronic myeloid leukemia without hitting leukemic stem cells, Haematologica (2009), doi:10.3324/haematol.2009.015271.
[28] F. Michor, T.P. Hughes, Y. Iwasa, S. Branford, N.P. Shah, C.L. Sawyers, M.A. Nowak, Dynamics of chronic myeloid leukaemia, Nature 435 (2005) 1267–1270.
[29] I. Roeder, M. Horn, I. Glauche, A. Hochhaus, M.C. Mueller, M. Loeffler, Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications, Nat. Med. 12 (2006) 1181–1184.
[30] M. Ichimaru, T. Ishimaru, M. Mikami, Y. Yamada, T. Ohkita, Incidence of leukemia in a fixed cohort of atomic bomb survivors and controls, Hiroshima and Nagasaki October 1950–December 1978, Technical Report RERF TR 13-81, Radiation Effects Research Foundation, Hiroshima, 1981.
[31] D. Dingli, J.M. Pacheco, A. Traulsen, Multiple mutant clones in blood rarely coexist, Phys. Rev. E Stat. Nonlin. Soft. Matter Phys. 77 (2008) 021915.
[32] M. Loeffler, K. Pantel, H. Wulff, H.E. Wichmann, A mathematical model of erythropoiesis in mice and rats. Part 1: structure of the model, Cell Tissue Kinet. 22 (1989) 13–30.
[33] C. Colijn, A.C. Fowler, M.C. Mackey, High frequency spikes in long period blood cell oscillations, J. Math. Biol. 53 (2006) 499–519.
[34] H. Haeno, R.L. Levine, D.G. Gilliland, F. Michor, A progenitor cell origin of myeloid malignancies, Proc. Natl. Acad. Sci. USA 106 (2009) 16616–16621.
[35] T.H. Brummendorf, T.L. Holyoake, N. Rufer, M.J. Barnett, M. Schulzer, C.J. Eaves, A.C. Eaves, P.M. Lansdorp, Prognostic implications of differences in telomere length between normal and malignant cells from patients with chronic myeloid leukemia measured by flow cytometry, Blood 95 (2000) 1883–1890.
[36] B.J. Druker, F. Guilhot, S.G. O'Brien, I. Gathmann, H. Kantarjian, N. Gattermann, M.W. Deininger, R.T. Silver, J.M. Goldman, R.M. Stone, F. Cervantes, A. Hochhaus, B.L. Powell, J.L. Gabrilove, P. Rousselot, J. Reiffers, J.J. Cornelissen, T. Hughes, H. Agis, T. Fischer, G. Verhoef, J. Shepherd, G. Saglio, A. Gratwohl, J.L. Nielsen, J.P. Radich, B. Simonsson, K. Taylor, M. Baccarani, C. So, L. Letvak, R.A. Larson, Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia, New Engl. J. Med. 355 (2006) 2408–2417.
[37] S.B. Marley, M.Y. Gordon, Chronic myeloid leukaemia: stem cell derived but progenitor cell driven, Clin. Sci. (London) 109 (2005) 13–25.
[38] B. Peng, P. Lloyd, H. Schran, Clinical pharmacokinetics of imatinib, Clin. Pharmacokinet. 44 (2005) 879–894.

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