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The allometry of chronic myeloid leukemia

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ABSTRACT

Chronic myeloid leukemia (CML) is an acquired neoplastic hematopoietic stem cell (HSC) disorder characterized by the expression of the *BCR-ABL* oncoprotein. This gene product is necessary and sufficient to explain the chronic phase of CML. The only known cause of CML is radiation exposure leading to a mutation of at least one HSC, although the vast majority of patients with CML do not have a history of radiation exposure. Nonetheless, in humans, significant radiation exposure (after exposure to atomic bomb fallout) leads to disease diagnosis in 3–5 years. In murine models, disease dynamics are much faster and CML is fatal over the span of a few months. Our objective is to develop a model that accounts for CML across all mammals. In the following, we combine a model of CML dynamics in humans with allometric scaling of hematopoiesis across mammals to illustrate the natural history of chronic phase CML in various mammals. We show how a single cell can lead to a fatal illness in mice and humans but a higher burden of CML stem cells is necessary to induce disease in larger mammals such as elephants. The different dynamics of the disease is rationalized in terms of mammalian mass. Our work illustrates the relevance of animal models to understand human disease and highlights the importance of considering the re-scaling of the dynamics that accrues to the same biological process when planning experiments involving different species.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder (Fialkow et al., 1977; Goldman, 2004) that originates in a hematopoietic stem cell (HSC). The disease is characterized by the Philadelphia chromosome [t(9;22)(q34;q11)] (Rowley, 1973), a translocation that brings the *C-ABL* proto-oncogene, normally present on chromosome 9, near the major breakpoint cluster region (*BCR*) on chromosome 22. The *BCR-ABL* fusion gene that results leads to the aberrant expression of the *ABL* kinase (Groffen et al., 1984) and transformation of a HSC to a leukemic stem cell (LSC). Animal models suggest that aberrant expression of *BCR-ABL* in HSC may be enough to explain the chronic phase of the disease (Daley et al., 1990; Zhao et al., 2001). Proof that CML arises within a HSC is provided by the observation that *BCR-ABL* is found in both myeloid and lymphoid cells, including a small fraction of T and NK cells (Martin et al., 1980). CML is not unique to humans, and has been described in several other species including dogs, cats and rodents (Frith et al., 1993; Leifer et al., 1983; Pollet et al., 1978; Thomsen et al., 1991) although the exact incidence of this disease in non-human species is not known. In this work, we investigate the chronic phase of CML across terrestrial mammals.

In previous papers, we have developed a model for the architecture of hematopoiesis in humans (Dingli et al., 2007b), employed allometric principles to relate blood formation in humans to other mammals (Dingli and Pacheco, 2006; Dingli et al., 2008a, c) and analyzed the dynamics of CML in humans based on this architecture (Dingli et al., 2008b). This allowed us to determine the number of active HSC as well as the number of cells on each level of differentiation as a function of mammalian mass. Here, we combine our previous work on the dynamics of CML in humans with allometric ideas, assuming a common architecture of hematopoiesis in mammals that relates HSC to circulating blood cells. For the first time, this enables us to make hypotheses on the incidence and dynamics of CML in non-human mammals, which are of great interest to infer details of the disease from animal studies.

The number of HSC that contribute to hematopoiesis increases with mammalian size, scaling with the mass of adult mammals as $N_{SC} \sim M^{3/4}$ (Dingli and Pacheco, 2006). In a healthy adult human ($M \sim 70$ kg), approximately 400 HSC, each replicating on average once per year (Buescher et al., 1985; Dingli and Pacheco, 2006) are responsible for the daily marrow output of $\sim 3.5 \times 10^{11}$ cells. This process is disturbed in CML leading to an increased marrow output with $\geqslant 10^{12}$ cells/day (Holyoake et al., 2002). In CML, the

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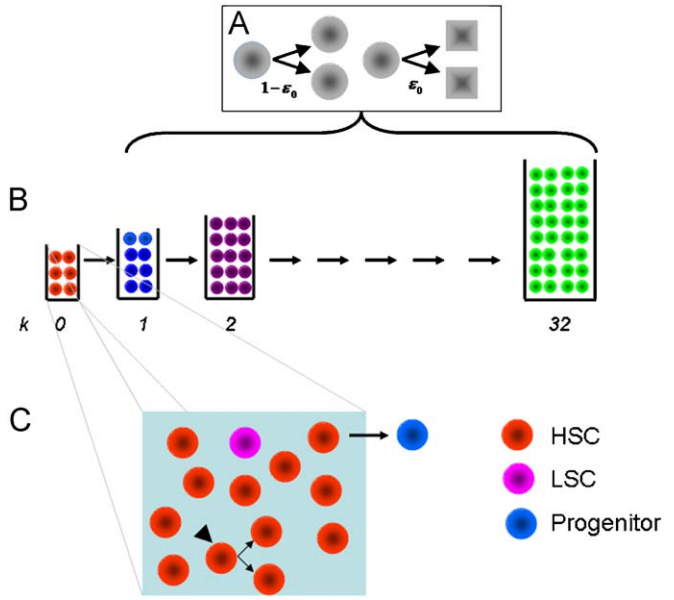

Fig. 1. The dynamics of hematopoiesis. (A) With the exception of HSC (see C), when a cell divides, the two daughter cells either differentiate with probability ε or self-renew with probability $1-\varepsilon$. (B) Differentiated cells move to the next downstream compartment. A total of 32 compartments mediate HSC and circulating blood cells. Under normal hematopoiesis, a steady flow of cells takes place "from left to right" across all compartments. (C) HSC occupy the earliest and smallest compartment. Their population is constant and at any one time, a cell is chosen for reproduction (double arrow) and another cell is chosen for export, thereby taking the path of differentiation by becoming a progenitor cell. In CML, the LSC have no fitness advantage and they are selected for reproduction or export with the same probability as normal HSC.

HSC pool is not expanded (Jamieson et al., 2004; Udomsakdi et al., 1992) and *BCR-ABL* expression does not give a fitness advantage to the LSC compared to HSC (Huntly et al., 2004). Thus, after the appearance of the first LSC, the expansion into a clone can only occur via neutral drift (Fig. 1). Hence, clonal expansion of LSC is intrinsically less likely and will take longer with increasing mammalian mass, despite the fact that the expected lifespan also increases with mass (Lopes et al., 2007). In contrast, *BCR-ABL* expression in progenitor cells gives them a fitness advantage due to a higher probability of self-renewal (Gordon et al., 1998; Marley and Gordon, 2005) that enables them to expand, leading to myeloproliferation and increased bone marrow cellular output (Fig. 1). As current evidence suggests, CML is mostly driven by progenitor cell expansion (Gordon et al., 1998; Marley and Gordon, 2005), despite originating in the HSC pool.

Hematopoiesis can be metaphorically represented by a hierarchical multi-compartmental model connecting HSC to circulating blood cells. Each compartment represents a different stage of differentiation of blood cells, as illustrated in Fig. 1. At the root of hematopoiesis lie the HSC. Under normal conditions, hematopoiesis corresponds to a state of dynamic equilibrium in which cells "move" from one compartment to the next as they become increasingly differentiated (Dingli et al., 2007b). In this work, we show how allometric scaling principles provide a rationale for the scattered information that is known to date on CML in mammals, leading to a unified view of CML dynamics across all mammals.

2. Mathematical model

Here, we first recapitulate our previous work on mathematical modeling of hematopoiesis and CML. Combining this model with allometric principles, we make quantitative predictions on the disease in other mammals in Section 3.

2.1. Allometric characterization of mammalian species

In biology, many observables related to the circulatory system (generally denoted by Y) scale with the mass M of the organism as $Y = Y_0 M^a$. In many instances, the exponent a is a multiple of 1/4 (Banavar et al., 1999). One of the best studied examples is the basal metabolic rate of adult species (R) which scales as $R = R_0 M^{3/4}$. This means that *in vivo*, cells replicate at a rate (B_c) directly related to the mass-specific basal metabolic rate $B_c = B_0 M^{-1/4}$ (West et al., 2002). For the purposes of our analysis, a given mammalian species is characterized by its average adult mass. In adult mammals, the number of HSC at the root of hematopoiesis (N_{SC}), also scales allometrically with their mass as $N_{SC} = N_0 M^{3/4}$ (Dingli and Pacheco, 2006). The scaling of N_{SC} suggests that hematopoiesis in a mouse ($M \approx 25\,\mathrm{g}$) may be maintained by a single or very few HSC (Lemischka et al., 1986), whereas in humans ($M \approx 70\,\mathrm{kg}$), approximately 400 HSC ensure a daily production of $\approx 3.5 \times 10^{11}$ blood cells in a multi-compartmental process of amplification and differentiation (Dingli et al., 2007b). In an elephant (*Elephas maximus*, $M \approx 4500\,\mathrm{kg}$), nearly 10^4 HSC are necessary to maintain hematopoiesis. The respective replication rates for the HSC are approximately 8 times per cell per year (~8/year) in the mouse, ~1/year in humans and ~0.3/year in the elephant, following the scaling of B_c above with $B_0 \approx 2.9\,\mathrm{kg}^{1/4}$ year, calibrated using the replication rate of human HSC. We further characterize the expected species-specific life-span by $\mathrm{L} = \mathrm{L}_0 M^{1/4}$ ($L_0 \approx 8.6\,\mathrm{kg}^{1/4}$ year) calibrated assuming a 4500 kg Asian Elephant has a lifetime of 70 years (Lopes et al., 2007).

2.2. Normal hematopoiesis and CML

Hematopoiesis can be considered as hierarchically organized into a multi-compartmental process in which cells in each compartment are in a given stage of differentiation (Michor et al., 2003). Our results are based on the assumption that the hierarchical organization of cell division and differentiation that characterizes mammalian hematopoiesis remains unchanged across mammals (Dingli et al., 2008c). At the root of the process lie HSC, and as differentiation occurs, cells move successively to downstream compartments, as illustrated in Fig. 1. The flow of cells between consecutive compartments ensures a steady output of cells that is regulated by cytokines. In this process, after each cell division, the daughter cells in compartment k differentiate and move to the next downstream compartment $(k+1)$ with probability ε, or they are retained in compartment k with probability $1-\varepsilon$ (Fig. 1A).

Thus, the number of cells in compartment k can be approximated as

$$\frac{d}{dt}N_k = -(2\varepsilon - 1)r_k N_k + 2\varepsilon r_{k-1} N_{k-1} \qquad (1)$$

Under stationary conditions, we recover normal hematopoiesis (Dingli et al., 2007b). In this case, we have, $\varepsilon \equiv \varepsilon_0 = 0.85$, implying that cells have a *limited* ability for self-renewal ($1-\varepsilon = 0.15$) and are more likely to differentiate and move to a downstream compartment (Dingli et al., 2007b). The rate of replication of cells, as well as the average number of cells in each stage of differentiation, increase exponentially across the $K = 32$ compartments that link HSC to the circulating blood cells (Dingli et al., 2007b), as illustrated in Fig. 1B.

Cell dynamics within the HSC pool can be described by a neutral Moran process (Fig. 1C). At each time step, a cell is randomly chosen for reproduction and this is followed by the random selection of a cell for export (that is, the cell moves into the next downstream compartment) so that the size of the HSC pool remains constant. In the case of CML, the appearance of a LSC does not alter the stochastic dynamics, since *BCR-ABL* does not give the LSC a fitness advantage (Huntly et al., 2004) and the LSC clone can only expand by neutral drift (in the absence of new mutations).

The appearance of the first LSC within the HSC pool disturbs normal hematopoiesis. The progeny of the mutant cell that move to the next downstream compartment have a higher self-renewal capability ($\varepsilon_{CML}<\varepsilon_0$), estimated at $\varepsilon_{CML}\sim 0.72$ (Dingli et al., 2008b). This gives the mutant cells an effective fitness advantage (Dingli et al., 2007a). As a result, in humans, the progeny of one LSC lead to myeloproliferation and marrow output $>10^{12}$ cells/day with a time lag of up to ~5 years. This time decreases as the number of LSC driving the disease is increased.

We can model disease dynamics by approximating the differentiation process in each compartment k by a differential equation for the number of CML cells N_k,

$$\frac{d}{dt}N_k = -(2\varepsilon^{CML}-1)r_k N_k^{CML} + 2\varepsilon^{CML} r_{k-1} N_{k-1}^{CML} \quad (2)$$

Due to $\varepsilon_{CML}<\varepsilon_0$, CML cells have a reproductive advantage compared to normal cells in each compartment. Ultimately, this leads to a higher bone marrow output. We solve Eqs. (1) and (2) numerically with a constant number of HSC, $N_0^{CML}=\text{const.}$, to compute the time until the normal bone marrow output increases four-fold, which is the condition for diagnosis of the disease in humans (Holyoake et al., 2002).

We apply this model of CML dynamics to different mammals by scaling the process across species, given the mass scaling of the active stem cell pool, the overall rate of cell replication and the species expected lifespan. We follow the dynamics for the respective mammal. Diagnosis required a sustained increase in bone marrow output of ~4 times normal as in the human condition (Holyoake et al., 2002).

3. Results

3.1. The number of LSC driving the disease

We have previously determined that between 1 and 8 LSC are enough to explain disease dynamics in chronic phase CML in humans (Dingli et al., 2008b). Since one LSC is enough to lead to diagnosis in humans, for smaller mammals, one LSC will *always* be sufficient to induce disease (Daley et al., 1990; Minami et al., 2008) given their smaller number of HSC contributing to hematopoiesis. However, for larger mammals, the situation can reverse. For example, an elephant with a mass of ~4500 kg has ~9100 HSC contributing to blood formation. Each of these cells replicates, on average, once every 3 years (Dingli and Pacheco, 2006). The large number of active HSC in the elephant confers it a significant risk of acquiring a mutant cell carrying the *BCR-ABL* oncoprotein (Dingli et al., 2008a). However, once this single mutation arises, the probability that it develops into a sizeable clone is small since it can only expand by neutral drift in a large pool of HSC (Dingli et al., 2008a). Moreover, the impact of such a cell on hematopoietic output will be small compared to smaller animals (our results show that marrow output essentially doubles, in contrast to humans with CML where it can increase by a factor of 4 or to mice, where it can increase at least 10-fold), given the relative contribution of a single LSC and its progeny to the overall marrow production. Consequently, and unlike humans, an elephant will thus reap the benefit of a larger HSC population that protects it from *neutral* clonal evolution (Lopes et al., 2007): Assuming CML in elephants to be biologically similar to that in humans, our results indicate that at least 3 LSC must be present in the elephant for the disease to be diagnosed within its lifetime (see Fig. 2A).

3.2. Transit times

We define the cell transit time as the time between the occurrence of the first mutation in a HSC and the appearance of progeny in the circulation. This time will be different across mammals, although it also generally scales allometrically, i.e. as $M^{-1/4}$. The minimum transit time is easily estimated assuming that cells always move into the downstream compartment upon replication. This leads to the sum of the average lifetime of each cell type in the corresponding compartment, that is,

$$T_{\min} = \frac{1}{B_c}\sum_{k=1}^{32}\frac{1}{\eta^k} \approx 1.28M^{1/4}$$

(with time in years, mass in kilograms and $\eta = 1.27$ across mammals). At the other extreme, given the fact that CML progenitors usually self-renew more often than normal progenitors in each compartment (Brummendorf et al., 2000; Dingli et al., 2008b), we can estimate an upper bound simply by scaling $T_{\min}$ with the factor $(2-\varepsilon_{CML})$; this ignores that cell number increases in each compartment contributing to an overall faster transit time. Nonetheless, this upper bound also leads to an allometric scaling relation for the transit time

$$T_{\max} = \frac{2-\varepsilon_{CML}}{B_c}\sum_{k=1}^{32}\frac{1}{\eta^k} \approx 1.70M^{1/4}$$

Naturally the transit time will be shortest for the mouse (~6 months), while for humans it will take approximately 3.8 years, being longest for the elephant where it will take on average ~11 years. It is noteworthy, however, that this transit time is usually shorter than the time necessary for diagnosis after the appearance of the first LSC since, depending on the mammal, the clone may have to expand and its progeny reach a critical threshold for the diagnosis to be established.

3.3. CML is CML in all mammals

It is estimated that the time from the appearance of the first LSC in humans to the diagnosis of CML is 3–5 years (Ichimaru et al., 1981). In a mouse, one LSC is enough to lead to a rapidly fatal illness since the pool of stem cells contributing to blood formation is so small (Daley et al., 1990; Lemischka et al., 1986). Using the scalings defined in the methods for the cell replication rates, and assuming that the biology of CML remains unchanged across mammals, we estimate that starting with 1 LSC the average time for diagnosis of CML is ~4 months for a mouse. Similarly, in a human being, a few LSC (1–8) are enough to drive CML with the typical time scales observed (Dingli et al., 2008b) (Fig. 2B). However, in an elephant a single LSC will not be able to contribute sufficiently to induce disease and only if the number of LSC increases to >3 will CML be diagnosed. Although the expansion to 3 cells (which will occur only with probability 1/3) will on average only take ≈3 years in the elephant, the probability of diagnosis is small during the lifetime of the animal, because even 3 cells will require ~30 years to lead to disease (Fig. 2A). Again, neutral evolution among stem cells will protect the elephant from such a process since it is very difficult for the LSC clone to expand in the

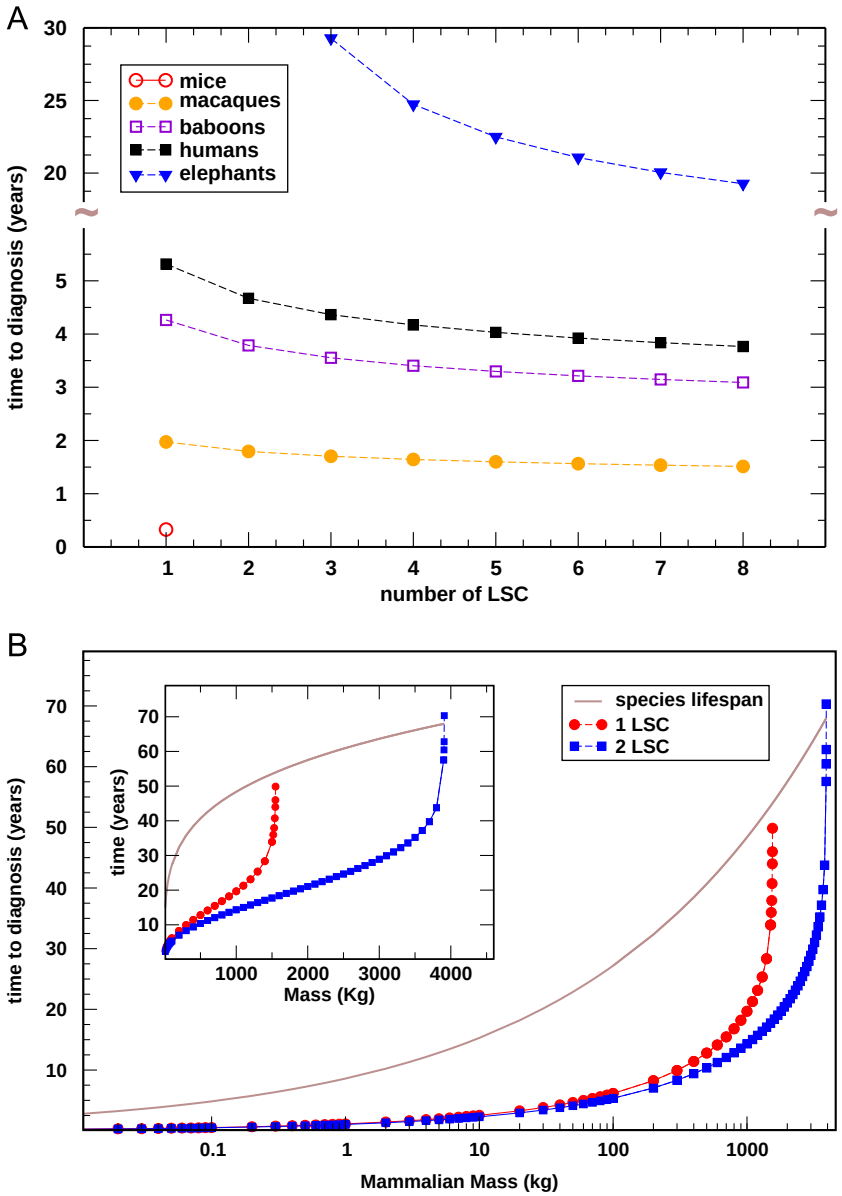

Fig. 2. CML diagnosis across mammals. (A) We show the time required to diagnose CML assuming the disease is driven by a constant number of LSC. We employ the model developed in Dingli et al. (2008b) scaling the cell replication rates and compartment sizes allometrically, as defined in the methods. We plot data for various mammals studied recently in the medical literature in connection with hematopoiesis. (B) Given the allometric scaling of expected lifespan defined in the methods, we use the model developed in Dingli et al. (2008b) (rescaled for each value of the adult mass) to calculate the time for diagnosis as a function of mass assuming CML is driven by 1 (circles) or 2 (squares) LSC at all times. The crossing of the data with the curve for the lifespan defines the theoretical limit of mammalian size for which diagnosis of CML can be reached within the animal lifespan. The inset is the same plot on a linear scale to emphasize the larger mammals while the main plot encompasses the whole spectrum of mammals from the smallest shrew to the elephant.

stem cell compartment in the absence of a fitness advantage. Since the probability that a single mutant LSC undergoes extinction is given by $1-N_{SC}^{-1}$, spontaneous elimination of the clone is much more likely in elephants than in humans or mice.

A mutant cell is only relevant as long as it leads to disease and, in this respect, mutations in HSC can be highly problematic, given the potential impact of those mutations across the hematopoietic tree. Interestingly, the transit time starting with 1 LSC, when expressed in terms of the expected lifespan of the mammal, remains invariant across mammals, implying that *BCR-ABL* has the same biological effect across species, thus providing an allometric rationale for the use of laboratory animals to study human disease.

4. Discussion

BCR-ABL expression is both necessary and sufficient to explain the chronic phase of CML (Daley et al., 1990; Zhao et al., 2001). The only established cause of CML is radiation exposure (Ichimaru et al., 1991; Ichimaru et al., 1981) that could lead to the chromosomal translocation necessary [t(9;22)(q34;q11)] to start the disease. However, most patients with CML do not have significant radiation exposure suggesting that in the majority of patients, the translocation occurs due to a replication error. The mutation rate is very similar across mammals and so it seems reasonable to assume that CML can also occur spontaneously in other species. Indeed, the disease has been described in cats, dogs and rodents (Frith et al., 1993; Leifer et al., 1983; Pollet et al., 1978;

Thomsen et al., 1991). In this work, we assumed that the genomic location of *BCR* and *ABL* is such that they allow recombination for the fusion *BCR-ABL* product to be generated. We acknowledge that in some specific species this may not be possible, although this should not invalidate the overall scenario studied here.

The injection of syngeneic hematopoietic stem cells transduced with a retroviral vector coding for *BCR-ABL* leads to a myeloproliferative disorder that resembles CML in irradiated mice. Southern blot analysis proved that the disease was clonal and arising from one single HSC. The interval between injection of the cells and 'diagnosis' of a CML-like disorder was of the order of 8 weeks (Daley et al., 1990; Minami et al., 2008). This is half what our model predicts. The reason for this discrepancy is that mice injected with the transduced cells are not in a steady state—instead they are recovering from the conditioning insult and the marrow is reconstituting (Marciniak-Czochra et al., 2009). It is natural then to expect that the disease will exhibit faster dynamics than our model predicts under steady state conditions. Indeed, CML cells are sensitive to growth factors and cytokines such as IL-3 and G-CSF (Marley et al., 2003) that are expected to be elevated after stem cell transplantation.

Our model predicts that one LSC is enough to induce a disorder like CML in the mouse and this is supported by experimental evidence (Daley et al., 1990; Minami et al., 2008). Perhaps the readers will wonder how a single LSC can lead to CML in humans that are so much larger than mice. However, we wish to point out that 1 LSC is the minimum; in serious cases of human CML the number of LSC grows, on average, by 1 per year. Hence, one expects that many diagnosed patients will have more than one LSC. More importantly, the characteristic time scales of disease evolution are different—in humans it takes $\sim$5 years for a single LSC to give rise to disease manifestations. In the case of an elephant, a single LSC will not be able to lead to disease and we estimate that at least 3 LSC are necessary. This, in turn, constitutes a major advantage for this large mammal, since LSC can only expand by neutral drift and, in an active HSC pool of $\sim$10,000 cells, this is extremely difficult. Moreover, 3 cells will lead to a significant marrow output only after 30 years which is half of the elephant's expected lifespan. Therefore, the largest mammals would be expected to be 'protected' from CML (Lopes et al., 2007), given that LSC expansion proceeds via neutral drift: In the context of neutral evolution, larger is better for hematopoiesis.

The mathematical analysis presented provides additional credence to the use of animal models to understand human disease. Murine models are convenient since the disease dynamics are significantly faster and results that could be potentially life-saving can be obtained rapidly. However, the difference in dynamics is not only an experimental convenience—it must be taken into consideration when planning the experiments and capturing data. Otherwise, important events can be missed if mice are treated as little humans (Pacheco et al., 2008). The interval between observations must be adjusted appropriately and here the insights obtained from allometry become essential. The rate of bone marrow output in mice is quite different from that of humans and it is this overall difference in rates that dictates the way dynamics unfold for the same disease. In other words, the same molecular defect will unfold in a different time frame depending on the host animal.

A major question that remains to be answered is why CML is more common in humans compared to other species. The underlying reason could be the fact that humans live far longer ($\approx$75 years) than the allometric estimate for their lifespan ($\approx$25 years). Hence, our HSC cumulatively divide three times more than predicted by allometry (Dingli et al., 2008c) and thus the risk of acquiring the *BCR-ABL* mutation leading to disease increases three-fold. Moreover, the longer lifespan of humans allows the disease to progress and be diagnosed more often than in other mammals. Our extended longevity is a result of our ability to alter the environment through agriculture and, indirectly, the development of language that led to cultural evolution and the rapid dissemination of knowledge. This knowledge has enabled *Homo sapiens* to fight infections, reduce accidental deaths and curb perinatal mortality, the major causes of 'premature' death in the not too distant past. Unfortunately, the resulting increase in expected lifespan comes with the price of a higher cumulative risk of cancer, now the second most common cause of death in many countries. Therefore it makes intuitive sense that CML affects humans in the fifth or sixth decade of life, when the allometric estimate of human lifespan is exceeded (Jaffe et al., 2001).

In summary, we provide a unifying view of the chronic phase of CML across mammals. Under normal conditions, the disease starts from a single LSC that expresses *BCR-ABL*. The oncoprotein does not give an advantage to the LSC but to the progenitor pool that expands and takes over hematopoiesis. A disease like CML is rare in small mammals since their active HSC pool is small (Lemischka et al., 1986). However, the Philadelphia chromosome in the murine HSC leads to a fatal illness over the period of a few weeks. In humans, 1 LSC can lead to CML although the dynamics are slow and it will require $\sim$5 years for diagnosis. The largest mammals such as elephants are protected from CML since the LSC has to expand to lead to disease, a long journey given the animal's expected lifespan. Indeed, such expansion is most unlikely given that it occurs by neutral drift in such a 'large' pool of cells.

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