Lymphocyte kinetics in health and disease

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Quantitative understanding of immunology requires the development of experimental and mathematical techniques for estimation of rates of division and death of lymphocytes under different conditions. Here, we review the advantages and limitations of several labelling methods that are currently used to quantify turnover of lymphocytes in vivo. In addition to highlighting insights into lymphocyte kinetics which have recently been gained thanks to the development of novel techniques, we discuss important directions for future experimental and theoretical work in the field of lymphocyte turnover.

Introduction
Our understanding of cellular immunology has advanced on many fronts over the last few decades. As descriptive and mechanistic models have been developed, the need for complementary quantitative approaches has increased. Nowhere is this more true than in understanding lymphocyte turnover and the maintenance of lymphocyte homeostasis. The importance of understanding lymphocyte turnover lies not just in being able to make quantitative observations but also in being able to predict responses, determine constraints and develop new paradigms for vaccinology and therapeutics. It also gives insight into the impact of factors driving or modifying immune responses, and addresses key questions in understanding immunological processes such as:

- Why do T-cell immunological memory and protective levels of antibody sometimes persist for decades, but in other cases decline rapidly? Can we influence their duration?
- Does the survival of clones determine persistence of memory or does continued recruitment have a more important role? Do memory clones, which divide relatively frequently, become exhausted or are they protected?
- How are cell division and cell death linked?
- How does ageing influence lymphocyte kinetics? Does exhaustion of lymphocyte precursors have a role in immunosenescence?
- What determines whether cells live or die? What are the roles of stimulation (not enough or too much), failure to compete and ‘survival niches’?

Lymphocyte turnover can be influenced by many immunological or cellular factors (Table 1) and a large body of experimental data describing lymphocyte kinetics in different settings has emerged over the last few years. Such data are, however, only one part of the descriptive process; the other component is quantitative interpretation. For this, mathematical models are required to enable expression of data in meaningful, comparable parameters. This review highlights some of the key topics that were presented at a recent meeting on ‘Lymphocyte Kinetics in Health and Disease’ held in London, UK.

Although other methods, including analyses of Ki67 or Annexin V expression, T-cell receptor excision circles (TREC) and measurement of cells with chromosome damage or during T-cell reconstitution have provided valuable insights into T-cell dynamics, the primary focus of this article is on lymphocyte labelling studies. Our aim is to provide an overview of the ways in which labelling studies of lymphocyte kinetics are currently being used to increase our understanding of immunology, in addition to presenting some of the important unanswered questions and future directions for both experimental and theoretical work.

Basic immunology: memory and homeostasis
Investigation of lymphocyte kinetics has been applied to several aspects of normal in vivo human lymphocyte behaviour. The attribute of ‘memory’, for example, has been addressed using deuterium labelling in humans [1–5] (Box 1 and Figure 1), and confirmed previous observations [6] that memory T cells have higher turnover rates than naïve T cells. In mice using BrdU (bromodeoxyuridine) labelling, a similar turnover pattern is seen [7]. Memory T cells, however, are quite heterogeneous both phenotypically (i.e. surface markers expressed) and kinetically (i.e. rates of proliferation and death). For example, it has been shown

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The meeting website, which includes abstracts and presentations can be found at:
http://s106175301.websitehome.co.uk/idrn_new/events/previous/lymphocyte.php.
that effector-memory (CD45RO⁺CCR7⁻CD62L⁻) CD4⁺ T cells (TCM) divide more rapidly and have a shorter survival time than central-memory (CD45RO⁺CCR7⁺CD62L⁺) CD4⁺ T cells (TSEMRA) [2]. By contrast, within the CD8⁺ T-cell pool, two long-lived CD8⁺ memory T-cell subpopulations have been identified: TCM cells expressing IL-7Rα and TEMRA (CD45RA⁺) cells of which a large fraction expresses CD57 [8]. Thus, kinetic studies can be used to resolve the behaviour of different T-cell populations. Interestingly, immunological memory is turned into immunological amnesia by depletion of dividing T cells [9] despite the presence of quiescent T cells displaying a ‘memory’ phenotype, indicating that division per se is a crucial component of functional memory.

The example of regulatory T (Treg) cells demonstrates how different approaches yield complementary information. Findings from labelling studies in humans with deuterated glucose (i.e. rapid division and short survival of CD4⁺CD45RO⁺Foxp3⁺CD25hi Treg cells) are consistent with Ki67 expression (i.e. high expression, indicating active cell cycling) and telomere length (i.e. short, indicating multiple cell divisions). When combined with studies demonstrating shared clonality with effector/memory cells, these data indicate that Treg cells are derived predominantly from a pool of rapidly proliferating, highly differentiated memory CD4⁺ T cells [10]. Homeostatic, as opposed to antigen-driven, proliferation of CD8⁺ T cells has been further investigated using CFSE (carboxyfluorescein succinimidyl ester) labelling in a murine lymphopenia-induced proliferation model. Proliferative responses under such conditions were more consistent with a stochastic than a programmed-division model (i.e. even monoclonal T-cell populations demonstrated considerable heterogeneity in proliferative responses) [11].

Ageing and immunosenescence

It is known that ageing affects many immunological processes. For example, current vaccines are often less effective in the elderly than in young adults [12]. However, we have a limited understanding of why this is the case and what changes in the immune system as we age. Ageing has, in general, little influence on the average total rate of T-cell production (from the thymus and cell division in the periphery) and disappearance in humans [5], but recently produced CD8⁺ CD45RA⁺ T cells have a longer life span in elderly subjects compared to young adults [13], possibly because of the presence of large clones of primed CD45RA⁺ (cytomegalovirus-specific) cells [13,14]. By contrast, the average turnover rate of NK cells is decreased in elderly subjects compared to young adults [15]. Understanding the contribution of these kinetic differences to differences in immune function in the young and elderly requires further research.

The contribution of the thymus to the maintenance of naive T cells in mice has been investigated using a combination of deuterium labelling and thymectomy experiments. These studies have demonstrated that maintenance of naive CD4⁺ and CD8⁺ T cells in the periphery in mice is almost entirely because of thymic output rather than peripheral proliferation (Den Braber et al., unpublished), which, for CD8⁺ T cells, is consistent with BrdU studies in thymectomized mice, which indicated that naive CD8⁺ T cells have a long inter-mitotic time (almost 1 year) but a short half-life (as short as 7 weeks) [16]. In old mice (85-week-old), with low numbers of single-positive thymocytes, the average production rate of naive CD4⁺ T cells was found to be remarkably similar to that in young (12-week-old) mice, indicating that even in old mice the whole naive CD4⁺ T-cell pool is maintained by thymic output (Den Braber et al., unpublished). In a ‘soft’ thymectomy model, in which thymus output was temporarily blocked by depletion of dividing thymocytes and mature T cells, transient lymphopenia had little impact on the eventual number or composition of the T-cell pool in young (12-week-old) euthymic and thymectomized mice [15], but in old (18 month) mice homeostatic recovery was not achieved. What occurred was a compensatory oligoclonal expansion in memory CD8⁺ T cells, limiting the diversity of

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**Box 1. Stable-isotope labelling: heavy water and deuterated glucose**

Until recently, in vivo cell-kinetic studies in humans have been very limited because of concerns over the potential toxicity of the available labels (i.e. BrdU and CFSE). However, the advent of stable-isotope DNA labelling approaches has opened the way for widespread investigations in humans. The general principle of DNA-labelling studies is as follows: a compound containing a quantifiable stable isotope is introduced into the pool of DNA precursors for a defined time period. Stable isotope is incorporated into the DNA of S-phase cells and passed onto the daughters. The amount of labelled DNA is thus related to the number of cells in S-phase during the labelling period. Loss of label during the wash-out phase can be used to provide information about the disappearance of labelled cells. There are currently two approaches for delivering stable isotopes: labelling with deuterated glucose [44,45] and labelling with heavy (deuterated) water [50,54]. There are several methodological differences in how the label is administered and the data generated when using these two labels (Figure 1 in main text). Deuterated glucose is administered intravenously or orally for short (10 h-7 day) time periods. Blood samples are taken and the fraction of enrichment of deuterium over hydrogen in the ribose of DNA is calculated. The enrichment fraction is then divided by a constant (0.65 [45] or 0.60 [31,32]) to correct for intracellular dilution, and adjusted by the level of deuterated glucose enrichment achieved during the labelling phase as measured in plasma levels. The pool of body glucose is small and turns over rapidly and so efficient labelling and rapid off-labelling can be readily achieved. By contrast, heavy water is administered orally for relatively long periods of time (typically several weeks), permitting reliable labelling of slowly turning-over cell populations such as human naive T cells [4]. Because the level of heavy water in the body fluids (usually measured in urine) reaches its maximum and is lost from the body more slowly than deuterated glucose, correction for the actual level of heavy water in the body is required [4]. As with deuterated glucose, the level of enrichment of deuterium in the ribose part of DNA is calculated. However, in contrast with deuterated glucose, normalization is achieved by comparing the enrichment level in the population of interest with the maximal enrichment level of a rapidly turning-over cell population (e.g. granulocytes or thymocytes).
the T-cell population, in association with a more proinflammatory cytokine profile (Thomas-Vaslin et al. unpublished). Taken together, these studies indicate differences in kinetics of naïve and memory T cells in young and elderly humans and mice and encourage further studies to investigate the origin of these differences.

Viral infection and lymphocyte dynamics

Being able to reliably measure lymphocyte life spans not only contributes to our understanding of basic immunological processes but also reveals important insights into how these rates of turnover alter when the immune system is disturbed by infectious diseases. A key example is the increased rate of T-lymphocyte turnover typically observed in HIV infection. BrdU labelling studies indicate that HIV infection increases lymphocyte proliferation and death with increased entry of CD4+ and CD8+ T cells into a subpopulation of rapidly proliferating cells [17]. Analogously, stable-isotope labelling experiments consistently show increased T-cell turnover rates in HIV infection [18–20]. Increased CD4+ T-cell turnover has been attributed either to the general state of immune activation caused by the virus [21–23] or to homeostatic responses to the cumulative loss of CD4+ T cells [24], irrespective of the mechanism of cell death, which might itself be the outcome of many factors, such as the pro-apoptotic signals mediated by programmed death 1 (PD-1), T-cell immunoglobulin and mucin domain (TIM) and/or tumor necrosis factor receptor (TNFR). When the fate of deuterium-labelled cells was followed in HIV-positive patients labelled with heavy water, recently produced naïve and memory CD4+ and CD8+ T cells were found to be rapidly lost (Vrisekoop et al. unpublished), by contrast with young healthy volunteers, in whom recently produced naïve T cells disappeared very slowly, being preferentially incorporated in the naïve T-cell pool [4]. Together, these data indicate that the high levels of T-cell turnover in HIV infection are driven by the immune-activating properties of the virus rather than a homeostatic response to lymphopenia (Vrisekoop et al. unpublished).

In contrast to experimentally infected rhesus macaques and HIV-infected humans, natural simian hosts of SIV do not manifest CD4+ T-cell depletion and do not progress to AIDS despite similarly high levels of SIV replication. Interestingly, the life span of infected cells in unaffected natural hosts and humans seems to be very similar [25,26], arguing that the short life span of HIV or SIV-infected cells per se does not define pathogenicity. The important determinant of outcome seems to be the corresponding level of immune activation [27–30]. Heavy water studies demonstrate accelerated turnover of CD8+ T_CM in HIV-infected subjects with high viral load and an association of CD8+...
**Review**

**Trends in Immunology** Vol.30 No.4

**T_{CM}** depletion with viral load [8]. A therapeutic approach might therefore be to restore cell numbers by stimulation with IL-2. Kinetic analysis with deuterated glucose following IL-2 therapy in HIV-infected patients has revealed that the achieved increase in CD4⁺ (but not CD8⁺) T-cell numbers is primarily related to extended cell life span, rather than increased proliferation [31,32]. These studies provide a perfect illustration of the power of stable isotope labelling in distinguishing whether interventions affect the rate of cell division or cell death.

Another illustration of how estimates of lymphocyte kinetics can be used to further our understanding of the pathogen–host relationship comes from the field of HTLV-1 (human T-lymphotropic virus 1) research. HTLV-1 is associated with a range of diseases including adult T-cell leukaemia and HTLV-1-associated myelopathy. Short-term deuterated glucose labelling in HTLV-1-infected subjects showed increased rates of proliferation of both CD4⁺CD45RO⁺ and CD8⁺CD45RO⁺ T lymphocytes compared to uninfected controls [33]. The significant positive correlation of the proliferation rate of CD4⁺CD45RO⁺ T cells (the principal host cell for HTLV-1) with proviral expression and higher levels of CD4⁺CD45RO⁺ proliferation in patients with HTLV-1 associated myelopathy was integrated into a dynamic picture of HTLV-1 persistence with the aim of understanding the determinants of proviral load and disease risk [34,35]. This work indicated that, far from being latent as is often assumed, HTLV-I proteins are continuously expressed and that an individual’s proviral load and subsequent risk of developing disease is largely determined by the dynamic equilibrium that is reached between the virus and the host immune response.

**Leukaemia**

Lymphocyte homeostasis – the crucial balance between lymphocyte proliferation and death – is clearly disrupted in leukaemia. One much studied model is bovine leukaemia virus (BLV) which induces a B-cell leukaemia in infected sheep. In vivo BrdU and CFSE labelling showed that in BLV-infected animals, both B-cell proliferation and death are abnormal with elevated levels of B-cell proliferation in lymphoid tissue partially balanced by elevated B-cell death [36,37]. Preliminary evidence indicated that the spleen might be playing an important part in this balance. To investigate this possibility, in vivo CFSE labelling was used in animals before and after splenectomy [38]. Splenectomy abrogated the enhanced cell death associated with BLV infection and reduced the time to development of leukaemia by half, arguing for an important role of the spleen in controlling B-cell numbers and restraining progression of leukaemia.

Stable-isotope labelling has also proven to be an ideal way to distinguish between two heavily debated points of view with respect to B-cell chronic lymphocytic leukaemia (B-CLL). The dogma that B-CLL results from accumulation of B cells that fail to undergo apoptosis was challenged by heavy water labelling experiments, which showed that B cells in B-CLL patients do proliferate [39]. However, when compared with healthy individuals, the average proliferation rate of B cells in B-CLL patients was found to be nearly threefold lower than in healthy volunteers [40], indicating that impaired apoptosis might be more important than altered proliferation in driving CLL. Indeed, another study using heavy water showed that the largest difference in B-cell kinetics between B-CLL patients and healthy controls was a 10-fold lower rate of loss of labelled B cells in CLL patients [41]. CLL cells in bone marrow were found to have a higher level of deuterium enrichment than CLL cells in blood, but no difference was found between these two compartments in terms of Ki67-expression or pro- and anti-apoptotic profiles of CLL cells. This indicates that recently divided CLL cells are preferentially retained in the bone marrow even though the bone marrow is not the most important CLL proliferation site [41]. Other studies comparing blood and lymph nodes using Ki67 as a marker of proliferation have suggested that suppression of the pro-apoptotic gene Noxa in the lymph-node environment contributes to persistence of B-CLL at these sites [42]. Thus, heterogeneity in the proliferation and disappearance rates of B-CLL cells might be attributable to micro-environmental factors. Expression of CD38 on the B-CLL population, which is known to be an adverse prognostic factor, is associated with accelerated proliferation according to both Ki67 analysis [43] and plateau deuterium labelling during heavy water administration (C. Calissano, personal communication). However CD38⁺ and CD38⁻ B-CLL populations were found to have similar telomere lengths, indicating that CD38 expression is transient rather than defining a distinct subpopulation per se. The association with accelerated proliferation might explain why high CD38 expression predicts poor clinical outcome.

**Modelling**

Mathematical models are essential for the analysis and interpretation of lymphocyte-labelling data, especially when one is interested in quantitative estimates of rates of cell proliferation and death (Box 2). Without mathematical models, one is left with a simple qualitative interpretation of labelling data (e.g. peak labelling) that will not yield insights into processes that regulate cell division and cell death in different circumstances. Moreover, qualitative interpretations contain implicit assumptions that have, in the past, led to severe data misinterpretation. Different mathematical models that make different explicit assumptions about how cells are produced, labelled and lost have been proposed. The first approach was simply to look at the rate of label accumulation and estimate the fractional replacement (or cell turnover) rate [31,44,45]. These simple approaches, however, do not take into account any kinetic heterogeneity of cell populations and do not account for the fact that both cell division and loss contribute to the accumulation of labelled nucleotides during the pulse phase. Mohri et al. [20] developed a model (derived from a model to analyze BrdU data [46]) to interpret their studies of lymphocyte kinetics in healthy and HIV-infected individuals; in this model, cells can divide, die or enter the circulation from a ‘source’ [20]. When the model was fitted to the data, surprisingly, in many patients, the rate of cell death exceeded the rate of cell proliferation, indicating that at equilibrium, a large input of new, undivided cells from a source must compen-
Thus, two mathematical models ('source' and 'kinetic heterogeneity', Figure 2) have been used to estimate the rates of cell proliferation and death from stable isotope labelling data without additional investigations of which model is the most appropriate to use in given circumstances. Although the original formulation of the source model [20] yields different estimates of proliferation and death to the kinetic heterogeneity model, the source model can be rewritten to make it mathematically identical to the kinetic heterogeneity model (Ganusov et al., unpublished) by defining a new parameter, the average turnover rate [49]. The average turnover rate is different from the original proliferation and death-rate parameters of the source model, but is numerically identical to the average proliferation rate of the kinetic heterogeneity model. However, the interpretation of the two models, in particular the reason for the discrepancy between proliferation and death and the interpretation of the death rate measured, still differs markedly (see later).

**Future directions in the kinetic analysis of lymphocytes**

Despite numerous ways in which lymphocyte kinetics can be measured and applied, important questions still need to be addressed. Some of these are discussed here.

**Interpretation**

Although rewriting parameters into a single parameter – the average turnover rate [49] – resolves some of the inconsistencies between different models (Ganusov et al., unpublished), it does not resolve the issue of data interpretation. In the source model, the discrepancy (s) between the measured proliferation rate (p) and the measured loss rate (d) is because of thymic export or activation of resting cells [20]. In the kinetic heterogeneity model, this discrepancy is simply because the parameters pertain to two different populations: the average population and the recently divided population, respectively [47]. Thus, although both models can be rewritten to predict identical estimates of the average rate of turnover of lymphocytes in the population, the choice of model can crucially affect the interpretation of experimental results. For example, the observation that d and p for CD8+ T cells differ less in HIV-infected subjects compared to healthy controls [20] might either indicate that thymic production or activation of CD8+ T cells is decreased by HIV infection (source model), or that in HIV infection the entire CD8+ T cell pool more closely resembles the rapidly turning over subpopulation in uninfected people (i.e. that there is increased activation of CD8+ T cells in HIV infection [kinetic-heterogeneity model]). Technological developments to improve the sensitivity of DNA analysis will increase our ability to analyse the proliferative dynamics of rare phenotypic lymphocyte subsets [50,54], and this might enable us to evaluate kinetic heterogeneity directly.

**Discrepancy between stable-isotope methods**

Heavy water and deuterated glucose are both commonly used to quantify lymphocyte kinetics in vivo [4,8,19,33,39] (Box 1), but proliferation and death rate estimates using the two methods differ systematically, with higher values being obtained with deuterated glucose and with shorter
labelling times [51]. Because the labelled cell population contains a greater proportion of cells with slow turnover rates after long-term labelling, estimated death rates (of labelled cells) are expected to be higher in short-term compared to long-term labelling experiments [47]. However, there is no a priori reason to expect such systematic differences in terms of average production rates. These discrepancies cause two main problems. First, experiments that rely on the quantification of lymphocyte kinetics such as the calculation of the proportion of HTLV-I infected cells that are latent or the estimation of the time until a memory cell reaches the Hayflick cell division limit require accurate, reliable measurements of average proliferation and death rates. Second, the fact that the methods give inconsistent results undermines our confidence in both methods. The cause of the discrepancy in average turnover rates has not yet been identified but hypotheses currently being explored include: (i) saturation of a rapidly turning over subpopulation during relatively long labelling with heavy water, (ii) errors in estimation of the peak of labelling because of a lack of data points in short-term labelling experiments with deuterated glucose, (iii) errors caused by the assumption of a constant death rate throughout the course of the experiment and, (iv) errors in interpretation caused by labelled cell migration (Asquith et al. unpublished). Further experimental and theoretical data, it is hoped, will lead to a fuller understanding of the source of these discrepancies.

**An explicit kinetic heterogeneity model**

Models that are currently being used to interpret lymphocyte labelling data are empirical. One could generate a more mechanistic model by considering an infinite number of subpopulations, each independently in equilibrium. At first glance, such a model would be expected to have an infinite number of free parameters and therefore it would be impossible to fit to experimental data. However, by assuming a frequency distribution for the different turnover rates of the subpopulations, the number of parameters of the model could be reduced to one or two parameters (the mean and the shape parameter of the distribution) (Ganussov et al., unpublished). Difficulties still exist, however. For example, if the rate of cell proliferation is equal to the rate of cell death for each subpopulation (i.e. \( p = d \)), the model would predict no loss of BrdU label during the de-labelling phase (other than by label dilution), clearly inconsistent with experimental data [52]. Development of the model to account for subpopulations in addition to temporal heterogeneity (that occurs when cells change their kinetic properties over time [22]), and to encompass the dynamics of cells

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**Figure 2.** Cartoon illustrating the ‘source model’ and the ‘kinetic heterogeneity model’. The ‘source model’ assumes that the disappearance rate measured is the average disappearance rate of the whole population, the ‘kinetic heterogeneity model’ assumes that the disappearance rate measured is only the disappearance rate of the labelled population and that this is unlikely, in general, to be representative of the average population (because both the reason that the cell divided and the fact that it has divided means that it is atypical). Both models assume that the proliferation rate measured is the average proliferation rate of the whole population. These assumptions have two important corollaries: (i) the source model postulates a large input of cells (the majority of which are unlabelled) from an external source. For most cell populations studied to date (including total CD8+ T lymphocytes, total CD4+ T lymphocytes, CD8+ memory T cells, CD4+ memory T cells), the vast majority of new cells are produced by this external source, not by peripheral proliferation. The physiological correlate of such a large producer of cells that do not become labelled is unclear. (ii) The kinetic heterogeneity model postulates that, regardless of the model used to interpret the data, the measured disappearance rate is the disappearance rate of labelled cells and, as such, its value is dependent on the labelling protocol including choice of label and length of labelling period. In particular, for cell populations in which cells that have recently proliferated are more likely to die, shorter labelling periods would give rise to faster disappearance rates [47]. Different cell colours represent cells with different kinetics, which could arise because of differences in phenotype, cytokine microenvironment, division history or T cell receptor (TCR) activation.
in anatomically defined compartments, such as lymphoid tissues, lung and gut, is not trivial but could contribute substantially to our understanding of in vivo lymphocyte kinetics.

Conclusion
The combination of experimental techniques to measure lymphocyte turnover directly in vivo with mathematical modelling has yielded valuable insights into the mechanisms by which lymphocyte populations are maintained in health, and how infections might perturb the balance between production and death. This represents an area of fruitful collaboration between experimentalists and theoreticians. However, many issues and challenges remain unresolved in this branch of immunology and we hope that this review will stimulate future work to address these challenges.

Acknowledgements
The Lymphocyte kinetics in health and disease meeting would not have substantially to our understanding of in vivo lymphocyte kinetics.

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