Aging of the T Cell Compartment in Mice and Humans: From No Naive Expectations to Foggy Memories

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Aging of an organism can be defined as progressive, cumulative, and inevitable age-dependent alteration in structure and decline in function of multiple cells, tissues, and organs, leading to decreased ability to respond to stress and maintain homeostasis. Given that the ultimate inability to maintain homeostasis is death, this definition also links aging to its final outcome. Despite decades of research, the precise molecular mechanism(s) of aging were surprisingly difficult to define unambiguously. More than 40 theories of aging exist; many of them are not mutually exclusive, but few are clearly integrated and capable of explaining most of the observations (1). Although it is beyond the scope of this review to discuss different theories of aging in detail, a viable unified theory of aging would propose pathway(s) that simultaneously explain molecular, cellular, and organismal aging. Moreover, such pathways would operate across different species and within the members of a single species and be directly proportional to their life span and chronological age.

What we unambiguously know now comes close to a unified mechanism of aging. Aging is powerfully influenced by alterations in nutrient sensing and metabolism (2). Caloric restriction has been known for >75 y to extend the lifespan in model organisms by 30–40%. Similarly, >10 individual gene mutations, and at least two pharmacological interventions targeting the mTOR pathway [with rapamycin (3) and metformin (4)] were reported to extend the lifespan in model organisms by up to, or more than, 50%. All of these mutations/interventions affect and attenuate cellular growth and nutrient sensing and involve, directly or indirectly, the insulin/insulin growth factor pathway. Increased resistance to cellular stress has accompanied these interventions, leading to the “metabolism and cellular stress” theory of aging (5–7), which continues to garner support with time.

Immune system aging and T cell aging

Studying aging of the immune system is mandated by its substantial age-related decline and the concomitant increase in morbidity and mortality from infectious diseases in older adults (8–10). Overall, it is clear that aging of the immune system is a cumulative phenomenon, heterogeneous just as aging itself, and affecting individuals in the community at highly individualized and disparate rates. Given that the immune system is highly integrated and that, even within a single cell, signaling cascades are precisely spatially and temporally regulated, it is becoming evident that small dysregulations in individual steps of a series of signaling events and cell–cell communication steps can translate into major deficiencies in the overall immune defense.

With that in mind, distinct differences with aging have been identified in virtually every facet of the immune system examined, from the initial contact with a microbial pathogen all the way to its clearance and formation of protective immune memory or to coexistence with a persisting pathogen. Defects in various aspects of innate immune function were discussed recently (11–13). They include deficiencies in granulocyte, macrophage, and NK function (12, 13); diminished or functionally altered function of major innate sensing receptors and soluble systems (including complement) (14); and other age-related changes. However, our understanding of innate immune changes with aging remains incomplete, and some of the above changes lack the consistency and reproducibility
between different experimental systems and between different human subject cohorts.

By contrast, changes in adaptive immunity are much better defined and more reproducible. Humoral immunity and B cell alterations with aging were the subject of an excellent recent review (15). Therefore, neither innate immune nor B cell changes with aging are the topic of this text. Rather, I will focus on alterations in T cell function and maintenance with aging, both of which are among the most remarkable and most pronounced changes occurring within an aging immune system. Moreover, fixing T cell defects with aging often leads to restoration of functional and protective immunity in older organisms (16–19). Fig. 1 illustrates the multitude of steps necessary for the production and function of mature peripheral naïve and memory T cells, most, if not all, of which were shown to be altered in the course of aging.

**Thymic involution: the when, how, and why?**

Perhaps the most remarkable age-related change observed in the body is the involution of the thymus, the central organ orchestrating production of new T cells [age-related changes affecting the thymus were recently reviewed in depth in three expert reviews (20–22)]. This organ involutes relatively early in life in humans, with changes being evident even before puberty or, by some accounts, even soon after birth (23, 24). In mice, involution appears to be more gradual, but it is debatable whether the organ has any significant output after 15 mo of age in C57BL/6 laboratory mice, which are certainly the most studied animal model. Current data suggest that early thymic involution involves a primary thymic stromal defect, whereby one or more epithelial cell components, possibly the epithelial cell precursors/stem cells, are affected.

**FIGURE 1.** Multiple defects in the T cell compartment occur during aging. T cell development is altered in the BM during aging: BM stromal changes, as well as cell-intrinsic defects, cause hematopoietic stem cells (HSC) and progenitors to shift away from lymphoid lineages and toward myeloid lineages (right). Thymic T cell development is also altered during aging; there is evidence for decreased seeding from the BM, thymic involution, increased adiposity, and increased expression of proinflammatory cytokines. As a result, the T cell output from the aged thymus is significantly diminished. These developmental defects place stress on peripheral maintenance of T cell pools and T cell function in secondary and tertiary organs (left). In the peripheral lymphoid organs (spleen and lymph node) changes in thymic T cell production, along with increased expression of inflammatory cytokines, diminished network of follicular reticular cells (C. Surh, personal communication), and defects in Ag presentation result in a decrease in the naïve T cell pool, whereas the VM T cell pool expands (see Fig. 2), hampering responses to new infection. Cell-intrinsic defects, as well as impaired Ag processing and presentation, synergistically diminish T cell activation, as evident by decreased T cell proliferation and effector molecule expression. Such incompletely or defectively activated effector T cells migrate into tissues (e.g., gut, lung, skin), where decreased effector molecule expression and, potentially, altered trafficking, further contribute to the additive T cell defects with aging, resulting in defective T cell function that limits the response to infection.
by the process of aging. Expression of key differentiation and growth factors for thymic epithelial cells, such as the master transcriptional regulator FoxN1 and the keratinocyte growth factor, is altered with aging. Consistent with that, histological changes in the involuting thymus include decreased volumes of both cortical and medullary regions, disorganization of epithelial cell architecture and of the corticomedullary junction, and replacement of the stroma by adipose tissue. It remains unclear whether the last observation is due to true epithelial-to-mesenchymal transdifferentiation or to death/ lack of production of epithelial cells and expansion of adipose tissue (21). Adipose cells have the potential to produce a number of proinflammatory cytokines that can affect thymopoiesis. Subsequently, one finds an inverse correlation between thymic adiposity and thymic function; these are modulated in opposite directions by caloric restriction and obesity. Therefore, an increase in thymic adipocytes has the potential to accelerate or aggravate the loss of thymic function with aging, regardless of the exact origin of the fat cell increase with aging.

These early changes are compounded later in life by hematopoietic cell defects, which exhibit diminished differentiation toward the lymphoid lineage, with reduced generation of common lymphoid precursors and increased propensity toward myeloid differentiation (reviewed in Ref. 20). It is not clear whether, once differentiated toward the lymphoid lineage, aged precursors also face difficulties in seeding the old thymus, either because of cell-intrinsic defects or because of further age-related changes in stromal niches that may make them less receptive for seeding. The old precursors that make it into an old thymus have decreased differentiation potential, suggestive of true cell-intrinsic defects with aging. Thus, early T cell precursors (ETP) isolated from young and old mice were used to seed the fetal thymic organ cultures, and the number of ETP-derived cells from the old mouse was 10-fold lower than from the young mouse (25). Regardless of the number and exact nature of the above defects, they all lead to a single outcome: reduced thymocyte–stroma cross-talk, resulting in diminished export of new naive T cells into the periphery. Of interest, even once they are produced, recent thymic CD4+ emigrants from old mice may not be able to seed the peripheral pool as well as their younger counterparts (26).

Peripheral T cell maintenance with aging: who’s naive now?

Regardless of the exact mechanism(s) of involution, the result of thymic involution is diminished and, ultimately, negligible production of new naive T cells. A key question then is: how long is the thymus functional in different species? A recent article compared rates of naive T cell production in mice and humans (27), concluding that, relative to lifespan, the thymus in the mouse is a much more prominent contributor to the dynamics of the peripheral T cell pool, whereas, in humans, peripheral maintenance does most of the heavy lifting. This is consistent with the anecdotal observations on stress resistance of T cells from longer-lived species [e.g., human T cells undergo much less cell death than do mouse T cells following isolation and can be rested overnight in vitro or frozen and thawed without significant loss of function (28)], as well as with data that the peripheral CD8 T cell compartment could not be regenerated following Ab-mediated depletion in middle-aged (10–16-y old) cynomolgus macaques (Macaca fascicularis), regardless of whether the animals were thymectomized (29).

The lack of thymic production places significant stress upon peripheral maintenance of the remaining peripheral naive T cells, which need to protect the organism against new infections for the remainder of the lifetime, with no “cavalry” from the thymus coming to the rescue. Peripheral T cell maintenance relies on low-intensity, subthreshold stimulation via the TCR (essential for naive T cell maintenance) and/ or stimulation with the homeostatic cytokines IL-7 (necessary for survival of naive T cells but also can be used by memory cells) and IL-15 (essential for maintenance of memory cells) (reviewed in Ref. 30). In the process of this maintenance, which is normally composed of low-grade tonic signals that only very infrequently lead to cell division, cells maintain the phenotype and function consistent with their prior differentiation state. Importantly, a relative (e.g., lymphopenia) or an absolute excess of trophic cytokines leads to intensification of homeostatic proliferation and often results in a change in the phenotypic and functional status of the cells, so that naive cells assume a pseudo-memory phenotype. Several observations over the past 10 y concordantly indicated that the process of naive T cell homeostasis is profoundly affected by aging, with the changes aimed at maintaining a naive T cell pool, eventually leading to its further depletion and demise. For example, both human naive CD4 T cells (31) and nonhuman primate naive CD8 T cells (32) exhibit increased turnover with aging, indicative of increased homeostatic proliferation that has the potential to convert naive T cells into virtual memory (VM) cells. Formal proof that this is occurring on a large scale was subsequently found in mice; we showed that naive aging T cell precursors frequently assume VM phenotype and function in the absence of immunization (22). These findings were subsequently corroborated by other investigators (34, 35), and it was shown that, in wild-type mice, these VM cells dominate in the central memory (CM) compartment (35). Of interest, an accumulating body of evidence suggests that VM cells accumulating in old mice arise by mechanisms distinct from those that produce VM cells in young adult mice and also exhibit differences in function. VM cells in adult mice exhibit superior immediate effector function and proliferation compared with their true naive counterparts (36). They likely arise as a result of neonatal lymphopenia and are driven to proliferate and become VM in response to the excess of IL-7 in an absolutely or relatively “empty” mouse neonatal peripheral compartment (36), although in some mouse strains a portion of these cells also can arise in the developing thymus in response to IL-4 stimulation by NK-T cells (22). By contrast, VM cells in old wild-type mice exhibit signs of increased TCR avidity, as judged by elevated CD5 levels and decreased peptide/MHC dissociation rates (33). Moreover, in TCR-transgenic mice, these cells do not accumulate if additional TCR rearrangements are blocked by the absence of Rag genes (38), suggesting a role for TCR ligands in driving accumulation of these cells (22). Consistent with this, VM CD8 T cells from both TCR-transgenic and wild-type old mice show signs of functional alterations: they competently secrete T1-type cytokines, but they exhibit inferior proliferation relative to their true naive counterparts (38). Experiments

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are in progress to elucidate which Ags drive this TCR-dependent conversion and/or accumulation from naive to memory phenotype with aging.

In contrast to the clear numerical decline of naive CD8 T cells in aging mice (39) and humans (40), the CD4 T cell compartment appears to be numerically better conserved, because it shows no appreciable decrease across ages, at least in CMV- humans (40). However, the above VM conversion applies, at least in part, to CD4 T cells in old TCR-transgenic mice (38), and initial results suggest that wild-type CD4 T cells may show similar conversion with aging (V. Pulko, J.S. Davies, A. Wertheimer, J.L. Uhrlaub, and J. Nikolich-Zugich, manuscript in preparation), although it is not yet clear whether such cells are representative of populations generated in the course of antimicrobial responses to foreign Ags or are driven by homeostatic cues.

**FIGURE 2.** Self-renewal and differentiation of naive CD8 T cells into phenotypically and functionally distinct CD8 T cell subsets. Their phenotypic attributes, proliferative potential, and functional properties (cytokine production) are illustrated as increased (↑) or decreased (↓). Naive CD8 T cells are maintained by low-avidity TCR signaling following pMHC contact and IL-7 (upper right panel). Lymphopenia-driven homeostatic proliferation gives rise to neonatal VM CD8 T cells (middle right panel). These VM CD8 T cells can arise early (during the neonatal period) in the thymus (in response to weak TCR signals and IL-4 (37)) or in the periphery, from the first wave of thymic emigrants, in response to IL-7 (36, 103). Alternatively, over the lifespan, a different type of VM cells can arise in the periphery in response to near-threshold TCR signals that are likely stronger than TCR interactions that maintain naive T cells in the naive state (33–35, 38). Ligands promoting such VM cells could originate from self-Ags or microbiota; these cells accumulate with aging, unlike the neonatal-origin VM cells. Finally, in humans, we recently found a virtually naive subset (functionally differentiated yet lacking main effector markers) (V. Pulko, J.S. Davies, A. Wertheimer, J.L. Uhrlaub, and J. Nikolich-Zugich, manuscript in preparation), although it is not yet clear whether such cells are representative of populations generated in the course of antimicrobial responses to foreign Ags or are driven by homeostatic cues.

The T cell repertoire in the last third of life: intrinsic and extrinsic modifiers

Because the numbers of naive CD8 T cells decline with aging, one would expect that the diversity of the TCR repertoire follows suit. Indeed, there are notable examples of TCR diversity reduction with aging in mice and humans (reviewed in Refs. 44–46), initially detected based on anti-TCRVβ Ab staining (47, 48) and/or TR-BV CDR3 length (49) analysis (50, 51). Subsequent analysis included single-cell PCR (52) and high-throughput next-generation sequencing (53).
These studies, although informative, come with limitations. The mouse and most human studies analyzed the mobilized T cell repertoire, activated in response to immunization/infection. That carries the problem of age-related differences that may be related to Ag uptake, processing, presentation, co-stimulation, or other issues not primarily related to the maintenance of the naive T cell repertoire per se. A second limitation is that numerous studies simply analyzed total, unseparated CD4 or CD8 cell pools (or even worse, total T cell pools), using relatively low-definition techniques (usually CDR3 length polymorphism), providing some information on total TCR diversity; the caveat of this approach is that the changes in population representation with aging (relative dominance of less diverse memory T cells over the more diverse naive T cells) can drastically alter the results, and with that, data interpretation. Third, most, if not all, of the above studies, were limited to TCRVβ or TR-BV analysis. Finally, the field has not benefited from a definitive, well-controlled, high-throughput next-generation sequencing approach to inform us about diversity reduction with aging in individual subsets of T cells. In humans, the most stringent and well-controlled results in that regard were published recently on unseparated T cells and total CD4+ T cells (53), showing that TCRβ diversity roughly decreases in a linear manner with age and is already noticeable by the age 40 y, paralleling the decline in naive cells and consistent with data of Naylor et al. (31). Using individual analysis, these investigators found that there were <10,000 representative and shared TCR clonotypes and that their abundance within the top 100,000 clones correlated with overall TCR diversity and decreased with aging (53). Moreover, in octogenarians, these investigators found both an increase in the percentage of naive CD4 cells and an increase in TCR diversity relative to individuals around the mean age of 62 y. This strongly suggests selection/survival effects. The important point of this study is the finding of reduced diversity in total CD4 T cells, which are much less prone than are the CD8 T cells to decline numerically in human peripheral blood with aging (40). That suggests a genuine loss of diversity, rather than a simple replacement of diverse naive CD4 cells with less diverse CM and effector memory (EM) CD4 T cells with aging. Unfortunately, the above study (53) did not directly analyze purified major T cell subsets (naive, CM, EM) and did not account for the dramatic effects of CMV infection, which is known to significantly alter T cell pools with aging. A single mouse study published on a similar topic (54) suffers from similar limitations inasmuch as total CD4 T cells were analyzed from spleen and bone marrow (BM). Of interest, these investigators concluded that spleen, but not BM, exhibits reduced CD4+ T lymphocyte TCRβ diversity with aging; they further concluded that this was due to the concomitant expansion of a large number of clones.

Memory/EM TCRβ repertoire changes with aging were investigated by single-cell PCR in total mouse T cells in one mouse longitudinally, following lymphocytic choriomeningitis virus infection at 23 d and 15 and 26 mo postinfection, as well as in two additional animals at 26 mo postinfection (52); there was a drastic reduction in diversity, which, in one mouse, was complete (i.e., one clone was found in 100% of sequences). Although the scope of that study was not broad, the reduction in diversity was striking.

In infected humans and mice, the memory T cell repertoire with aging is under the extremely strong influence of the CMV virus (55), which infects 60–70% of humans in the Western hemisphere, with numbers being even higher in older adults. CMV induces strong (56, 57) and absolute inflation of both the EM CD8 and EM CD4 subsets (40, 58, 59), likely via direct stimulation of a wide repertoire of responding T cells with its complex peptides (60). It follows that humans (and other naturally or experimentally infected animals) will experience drastically different aging patterns in the presence and the absence of CMV infection, and that was shown for total CD8 TCR repertoire (61–63). In one study, this repertoire shrinkage was even linked with decreased residual lifespan (61), but the mechanistic underpinnings remain missing.

A single-cell approach, but with simultaneous sequencing of TR-AV and BV genes from human CMV-specific EM CD8 T cells (64), showed that individuals with high anti-CMV titers (usually used as a correlate of high CMV reactivation/activity) had lower CD8 T cell diversity in their anti-CMV response. That study did not evaluate aging as an independent variable, a critical and important question. Finally, several studies evaluated the impact of deliberate, controlled life-long mouse CMV infection upon immune responsiveness to third-party infection in old mice. All three studies found diminished CD8 responses to third-party infectious challenge in CMV-infected mice but not control mice or mice infected with acute microbial pathogens (39, 65, 66), and one of the studies found that CMV-infected mice exhibited a thoroughly different and nonoverlapping TCR utilization in these responses (39). Although it is unclear at what level CMV manipulates TCR utilization in old mice following lifelong infection, this result represents a stark example of external influences upon TCR diversity with aging.

Functional changes in old T cells

The above alterations in TCR repertoire could, by themselves, alter TCR avidity and, thereby, the functional output of old T cells. However, data on TCR avidity in aging are controversial. In the mouse, we described an increase in TCR avidity for pMHC in old mice both by direct pMHC dissociation assays and by CD5 levels (33). Consistent with that, we did not see a decline in functional avidity of old CD8 T cells responding to infection in mice (67) or to lifelong systemic HSV in mice (68) or rhesus CMV in monkeys (69). These measurements were made at the peak of primary response or during the course of ongoing EM responses; therefore, they may not reflect the responsiveness of naive T cells. Indeed, a list of functional and signaling defects in old T cells has accumulated over the past 40 y of research (reviewed in Refs. 70–72), including data on reduced T cell proliferation, effector function and synapse formation, impaired generation of early signaling intermediates, blunted induction of key fate-determining transcription factors, incomplete effector differentiation and effector molecule expression, and altered trafficking. Because this topic was extensively reviewed recently for both CD4 and CD8 T cells (71–73), I will not review it in exhaustive detail.

Rather, I will focus on the key question: to what extent are the above defects intrinsic to old T cells and to what extent can they be ascribed to defective Ag uptake, processing and presentation, suboptimal dendritic cell maturation/migration and/or problems in cytokine/inflammatory environment, all
of which have been documented to a greater or lesser extent? Certainly, in vivo whole animal testing and testing of unseparated T cell populations cannot resolve this question. Rather, most informative are the in vitro studies of minimally manipulated purified T cell subsets and in vivo transfers of the same purified subsets from old or adult mice into adult, T cell–deficient hosts. Focusing on these types of studies, one can discern clear patterns of cell-intrinsic defects in naive T cells. Thus, Miller et al. showed that in vitro–stimulated naive old CD4 T cells exhibit impaired cytoskeleton signaling, polarization, LAT and ZAP-70 recruitment, and CD3ζ phosphorylation all the way to the induction of NF-AT (reviewed in Ref. 74). Similar studies have not been performed in naive CD8 T cells. Swain and colleagues performed transfers of CD4 recent thymic emigrants between old and adult hosts and found that both the environment and the intrinsic T cell defects play a role in that setting (75). Haynes, Swain, and colleagues also documented that inflammatory cytokines can overcome some of the defects in Th cell function (16, 17), but the exact target for these cytokines has not been defined. In a mouse model of the West Nile virus, we showed that transferred total CD8 or CD4 T cells from an old donor do not confer protection upon a young Rag-knockout recipient, whereas adult donor T cell subsets provide substantial protection (76). This experiment did not purify naive T cells, and we subsequently showed that numbers of West Nile virus–specific (and all other) precursors decline by 60–90% with aging (33, 38); therefore, a true test of intrinsic defects on a per-cell basis remains to be done. However, at a minimum, this result strongly suggests that although CD8 T cells with increased TCR avidity (33) and/or CD4 T cells with increased cross-reactivity (41) (M.S. Kuhns, personal communication) accumulate/selectively survive with aging, they cannot provide sufficient immunity against viral infection. Finally, benign CD8 T cell clonal expansions, which arise as a result of unknown causes with aging in laboratory mice (47, 51) and whose emergence is enhanced by increased peripheral T cell turnover (77), adversely affected new primary responses if they were occupying the TCRβ family needed for the primary response (78). If such T cell clonal expansions are of known specificity for an infectious microorganism (e.g., a virus), their ability to respond to the virus in the late memory phase is often functionally compromised (79).

Memory T cell responses are also affected with aging, but in an asymmetrical manner. Specifically, memory responses generated in youth or adulthood appear to be much better preserved compared with those generated in old age from a primary response that is already riddled with different age-specific deficits (reviewed in Refs. 43, 80). Incomplete expansion and function during recall responses in old mice were observed in CD8 T cells responding to lymphocytic choriomeningitis virus (81), Listeria (67), or influenza (82), as well as in CD4 T cell responses to model Ags (83). By contrast, immunization of young adult individuals with vaccinia or infection with smallpox preserved robust CD8 T cell immune responses for decades, and perhaps for life (84), and they also provided strong protection against other poxvirus infections (85).

T cell trafficking with aging has been investigated in the human model, and it was shown that mobilization of cutaneous CD4 T cell immunity was defective in older adults, despite intact systemic immunity detected in blood (86); however, because of the limitations of the human model, it remained unanswered whether that defect is cell intrinsic. Much more research is needed on age-related T cell–trafficking defects.

Effector differentiation was conclusively shown to be defective in the CD8 and Th1 CD4 lineages in response to infection, with reduced expression of important effector cytokines, such as IFN-γ, TNF-α, granzyme B (76, 87), and IL-2 (88–90). Less is known about differentiation into other lineages, although it appears that the Th2 lineage is similarly impaired with aging (reviewed in Refs. 91, 92), with reduced production of GATA-3 (93), whereas Th17 function could be exacerbated (94) or decreased (95, 96). Regulatory T cells were found to be increased in old mice (97) and humans (98). Some studies suggested that aging increased the Th17 regulatory T cell ratio in humans (99), with an increased Th17 proportion; however, absolute numbers were not available, and functional differences were not confirmed in culture supernatants (99). By contrast, another study found a decreased proportion of Th17 cells under nonpolarizing conditions but a higher proportion under polarizing conditions (100). Overall, it remains unclear whether aging can lead to selective favoring of one of the functional T cell fates at the expense of others, and there is a dearth of studies on the function of Th9 and T follicular helper cells in aging.

Conclusions: what is wrong with old T cells and how to fix them?

As the reader could conclude from the above deliberations, numerous steps involved in generation, development, activation, effector differentiation, homeostasis, and trafficking are altered in T cells with aging (Fig. 1). Memory differentiation is less affected, but memory generated in the old age nonetheless ends up functionally inferior; it is only T cell memory generated in youth that remains relatively uncathed by the process of aging. From the standpoint of immune defense, it is important to reiterate that the above alterations need not be quantitatively remarkable to impact microbial clearance; small defects readily synergize along the same pathway to produce a multiplied and leveraged effect.

A practical question then arises: what can we do to improve T cell function with aging? A detailed discussion of that topic deserves a review by itself. However, it is warranted to say that our potential to intervene has never been greater. New adjuvants targeting specific innate sensors are being discovered and tested at an increasing rate (101), and several publications showed that TLR agonists (101), adjuvants (92), cytokines (17), and live attenuated vaccines (19) can all improve T cell responses and often protective immunity in old animals and humans. Transduction with specific transcription factors is also being attempted, but is practically less likely to be deployable. Finally, once naive T cells decline below a certain point, only T cell rejuvenation is able to replenish the lost reserve. The good news is that T cell rejuvenation is by no means impossible, because several treatments can impressively regrow an old thymus (102). The less good news is that thymic involution and loss of function with age is a complex and composite process, and it is now clear that single treatments are unlikely to restore the totality of function, including robust export of functional T cells to the periphery, to allow for improved immune defense (22, 102). The journey
to improving T cell function with aging, and in particular to fully rejuvenating thymic production and peripheral T cell performance, promises to be at the same time difficult, exciting, and highly rewarding.

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Disclosures

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