

REVIEW

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Clinical rationale for thymic restoration in adult immunosenescence

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Abstract

Age-related thymic involution is a central feature of immunosenescence and intersects with multiple “hallmarks of aging”, including genomic instability, telomere attrition, mitochondrial dysfunction, and chronic inflammation. The decline in thymic epithelial integrity and FOXP1-driven thymopoiesis reduces naïve T-cell output, contracts TCR repertoire diversity, and perturbs central tolerance, contributing to increased susceptibility to infection, cancer, and autoimmunity. These changes occur alongside broader immune-aging phenomena such as inflammaging and frailty and are reflected in poorer vaccine responses and altered outcomes to novel pathogens such as SARS-CoV-2. This review integrates mechanistic, preclinical, and human data to reassess the adult thymus as a therapeutic target. Higher-confidence domains for thymic restoration include cancer immunosurveillance, infectious disease vulnerability, vaccine responsiveness, and post-treatment immune reconstitution, supported by modeling of age-related disease incidence, transplant and HIV cohorts, and new observational links between radiographic thymic health, mortality, and immunotherapy outcomes. High-plausibility but less directly validated domains include autoimmunity, chronic herpesvirus control, HIV immunological non-responders, and post-acute infection syndromes such as long COVID, which share convergent patterns of T-cell dysfunction and persistent immune activation. The translational landscape spans hormonal and somatotrophic modulation (sex steroid ablation, growth hormone/ghrelin), cytokine and growth-factor strategies (IL-7, IL-22, KGF/BMP4, FGF21), cell- and tissue-engineering approaches leveraging thymic epithelial stem cells and FOXP1-reprogrammed stromal cells, and gene-therapy concepts such as intrathymic AAV delivery of FOXP1, AIRE, chemokines, and stromal-support pathways. Collectively, these data support the biological plausibility of adult thymus restoration but highlight that robust, domain-specific clinical benefits have not yet been demonstrated in controlled trials. Future work should prioritize harmonized structural and functional biomarkers, domain-focused interventional studies in high-risk populations, and combined strategies that situate thymus-directed interventions within broader efforts to modify immune and organismal aging.

Keywords Thymic regeneration, Immunosenescence, Thymic involution, FOXP1, Cancer immunosurveillance, Vaccine responsiveness, Immune reconstitution, Inflammaging, Thymic epithelial stem cells, Aging biology

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Background

The thymus is the primary site of T-cell development and central tolerance, yet it undergoes a characteristic program of age-related involution beginning in early adulthood [1–3]. Progressive loss of functional thymic epithelial tissue leads to reduced naïve T-cell output, contraction of TCR repertoire diversity, impaired generation of regulatory T cells, and perturbation of negative selection, thereby contributing to increased susceptibility to infection, cancer, and autoimmunity in later life [1, 3–7]. These changes occur within a broader landscape of aging biology that includes genomic instability, mitochondrial dysfunction, telomere attrition, epigenetic alterations, and chronic low-grade inflammation, which collectively drive immunosenescence and “inflammaging” [5, 8–10].

Classic studies of thymic structure and function documented the replacement of lymphoid and epithelial components by adipose and fibrotic tissue, with a decline in thymic cellularity and export that tracks closely with the age-associated rise in infection and cancer incidence [2, 3, 5, 7, 11–13]. More recent work has refined this picture, emphasizing that thymic involution is not a simple, irreversible atrophy but a dynamic process shaped by intrinsic transcriptional programs, systemic endocrine and metabolic inputs, and the emergence of age-associated epithelial states that both reflect and reinforce organ dysfunction [14–19]. At the same time, large-scale human studies have begun to reposition the adult thymus as a clinically relevant organ: radiographic measures of thymic health in asymptomatic adults predict all-cause mortality, lung cancer and cardiovascular events, and separate analyses in patients with cancer indicate that thymic status influences response to immune checkpoint blockade [11, 12, 20–22].

These converging lines of evidence suggest that thymic involution is a mechanistically important contributor to the age-associated burden of disease rather than a benign developmental epiphenomenon [3, 5, 8, 9, 11, 21, 23]. Mathematical modeling indicates that the decline in T-cell production with age is consistent with a substantial fraction of rising cancer incidence across multiple tumor types, although the model does not exclude parallel contributions from mutation accumulation, epigenetic drift, or other aging processes [11]. Observational data from solid organ transplant recipients, HIV infection, and thymectomy cohorts further demonstrate that sustained impairment of T-cell competence markedly increases cancer risk and infection-related morbidity [9, 12, 13, 21, 22, 24–28]. Within the broader framework of aging biology, the thymus therefore represents a plausible upstream node linking immunosenescence to multiple clinical domains, including cancer, infectious disease, autoimmunity, cardiovascular disease, neurodegeneration, and frailty [3, 5, 6, 8, 9, 11–13, 20, 23, 29].

The central premise of this review is that age-related thymic decline should be considered an actionable therapeutic target in adults. Mechanistic and translational data over the past decade have established: (i) that the involuted thymus retains epithelial stem and progenitor cells with multilineage potential; (ii) that endogenous regenerative pathways can be engaged by specific cytokines and growth factors; and (iii) that hormonal, pharmacological, cell-based and gene-based interventions can modulate thymic structure and output in animal models and early human studies [14–19, 22, 23, 30–42]. At the same time, emerging work has identified age-associated epithelial defects and inhibitory niches that may limit the efficacy of simple pro-regenerative strategies, and clinical trials have underscored that not all interventions are beneficial across all contexts [14–19, 23, 34, 36, 38, 39, 43, 44].

In this context, the aims of this paper are threefold. First, we synthesize current mechanistic understanding of thymic involution and regeneration, with particular emphasis on recent advances in human thymic epithelial stem-cell biology and stromal–immune crosstalk [14–19, 22, 23, 30]. Second, we map the clinical domains in which thymic restoration is most likely to deliver benefit, distinguishing established from high-plausibility and more speculative indications on the basis of available evidence [3, 5, 6, 9, 11–13, 20–25, 28, 29, 45, 46]. Third, we review existing and emerging thymus-directed therapeutic strategies, including their mechanistic rationale, preclinical support, and early clinical experience, and to propose priorities for future research and clinical translation [14–19, 22, 23, 31–42].

Scope and methodology

This narrative review synthesizes mechanistic, preclinical, and clinical evidence relating to thymic involution and its reversal in the context of adult immunosenescence. Literature was identified through PubMed, Scopus, and Google Scholar searches using combinations of the following terms: thymic involution, thymic regeneration, immunosenescence, FOXP1, thymic epithelial cells, thymic stem cells, inflammaging, immune reconstitution, thymectomy, and immune aging, with an emphasis on publications from 2015 to early 2026. Seminal earlier studies establishing foundational concepts in thymic biology, T-cell development, and immune aging were also included. Reference lists of key reviews and primary articles were screened for additional relevant sources. Clinical domains were classified into evidence tiers (established, high-plausibility, and speculative) based on the convergence of human observational data, mechanistic plausibility from preclinical models, and availability of interventional evidence, as described in section “[Therapeutic domains and evidence tiers](#)”. As a narrative review, no formal systematic search protocol, risk-of-bias

assessment, or meta-analysis was performed; the aim was to provide a comprehensive, critical synthesis rather than a quantitative summary of the literature.

Thymic biology, involution, and regeneration

T-cell development and thymic microanatomy

T-cell development depends on a specialized thymic microenvironment in which hematopoietic progenitors from bone marrow undergo sequential stages of differentiation, selection, and maturation [1, 3, 6, 7, 47]. Double-negative ($CD4^-CD8^-$) thymocytes enter the cortex, rearrange their TCR β -chain, and progress to the double-positive ($CD4^+CD8^+$) stage, where they undergo positive selection on cortical thymic epithelial cells that present self-peptide–MHC complexes [1, 7, 47]. Cells that successfully recognize self-MHC with appropriate affinity migrate to the medulla and are exposed to a diverse array of self-antigens presented by medullary thymic epithelial cells and dendritic cells, where high-affinity self-reactive clones are deleted and a subset is diverted into the regulatory T-cell lineage [3, 6, 7, 47]. This process depends critically on the transcription factor AIRE, which drives promiscuous expression of tissue-restricted antigens in medullary epithelial cells, and on intact three-dimensional organization of cortical and medullary compartments [3, 6, 7, 14, 17, 47].

Age-related thymic involution disrupts these processes at multiple levels. There is a gradual loss of thymic epithelial cells, particularly in the cortex, with replacement by adipocytes and fibroblasts, alterations in the composition and organization of medullary epithelial subsets, and changes in the vasculature and extracellular matrix [1–3, 6, 11, 14, 16–19]. Functionally, this translates into reduced output of naïve $CD4^+$ and $CD8^+$ T cells, diminished generation of new TCR clonotypes, and a shift in the peripheral compartment toward memory and senescent phenotypes [1, 3–6, 9, 11, 24, 25]. Deep sequencing studies demonstrate a progressive contraction in TCR repertoire diversity with age, including the loss of low-frequency clonotypes that may be particularly important for recognizing novel pathogens and tumor neoantigens [4, 5, 11, 24, 25]. In parallel, perturbation of negative selection and reduced Treg output allow autoreactive clones to escape into the periphery, contributing to the increased incidence of late-onset autoimmune disease [3, 5, 6, 47].

Molecular drivers of thymic involution

Multiple convergent mechanisms drive thymic involution. Declining expression of the transcription factor FOXN1 in thymic epithelial cells is a central event, as demonstrated by murine models in which enforced FOXN1 expression in aged thymi restores organ size, architecture, and thymopoiesis to a more youthful state

[14, 17, 30, 31, 35]. Human studies show that FOXN1 transcription declines with age and is associated with epigenetic changes, including increased promoter methylation [8, 14, 17, 35]. Other cell-intrinsic pathways, such as TBATA–Uba3–Nedd8 signaling, TGF- β pathway activation, and telomere attrition in epithelial cells, further constrain proliferative capacity and promote a shift toward fibrotic and adipogenic phenotypes [8, 14–19, 23, 41]. Beyond systemic metabolic inputs and FOXN1 loss, adipogenic replacement is governed by local, cell-intrinsic programs within the thymic stroma. Peroxisome proliferator-activated receptor- γ (PPAR γ) functions as a proadipogenic master regulator in thymic stromal cells, acting downstream of its upstream activator xanthine oxidoreductase, and its age-related elevation accompanies epithelial-to-mesenchymal transition and the induction of regulators such as FoxC2 and fibroblast-specific protein-1 [48]; experimentally, an adipocyte-lineage-specific constitutively active PPAR γ transgene is sufficient to induce ectopic thymic adipogenesis and reduce thymopoiesis [49], whereas genetic PPAR γ deficiency delays thymic senescence and sustains naïve T-cell output [50], establishing this axis as a non-redundant local driver rather than a passive marker. In parallel, age-associated down-regulation of Wnt4 and up-regulation of LAP2 α derepress PPAR γ and drive thymic epithelial senescence with adipose conversion, mirroring the molecular program of pre-adipocyte differentiation [51]. These local programs operate in concert with, and downstream of, systemic regulators of thymic adipogenesis—including Wnt-pathway attenuation, somatotrophic-axis decline, and rising sex steroids—positioning PPAR γ as the proximate intracellular effector through which systemic signals are executed [52]. Because these drivers act locally, purely systemic metabolic interventions may be insufficient to reverse established intrathymic fat replacement once the epithelial-to-adipocyte switch is engaged, which has implications for the design and expected efficacy of metabolically targeted therapies.

Systemic factors contribute in parallel. Rising sex steroid levels in puberty and adulthood accelerate thymic involution, whereas sex steroid ablation in rodents and humans can partially reverse involution and increase thymic output [3, 19, 32, 42, 53]. Age-related changes in the somatotrophic axis—declining growth hormone, IGF-1, and ghrelin signaling—as well as alterations in FGF21 and other metabolic mediators, modulate thymic epithelial survival, proliferation, and adipogenesis [9, 15, 19, 23, 42]. Chronic low-grade inflammation and accumulation of senescent cells, characteristic of “inflammaging”, further disturb thymic stromal homeostasis and may promote the emergence of dysfunctional epithelial states [6, 8–10, 23, 43, 54].

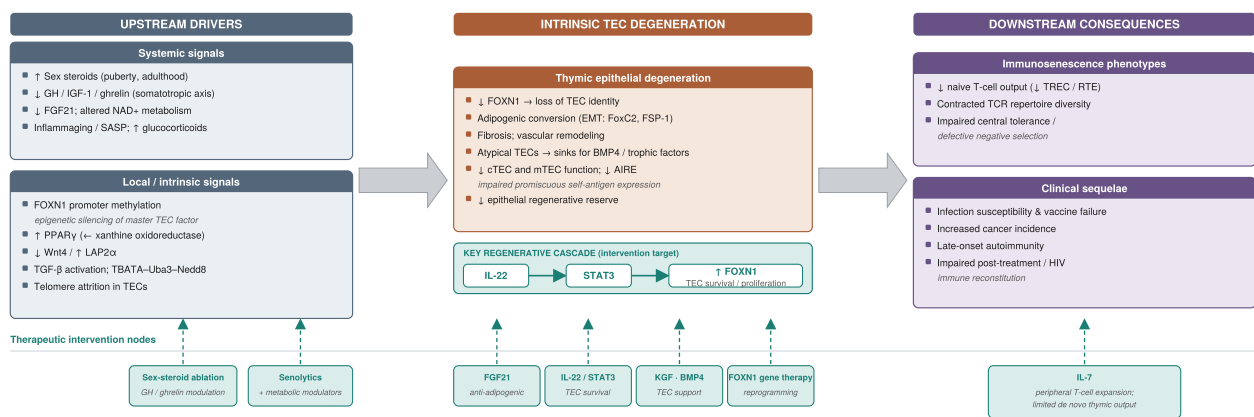
Recent high-resolution mapping of the aging thymus has revealed that involution is not purely atrophic but also involves qualitative changes in epithelial populations. Single-cell and spatial transcriptomics have identified age-associated atypical thymic epithelial cells that form dense epithelial clusters devoid of thymocytes, act as sinks for growth factors such as BMP4, and expand after injury, thereby disrupting trophic signaling and regeneration [14, 16–19, 36, 38, 39]. These findings provide a mechanistic explanation for the observation that thymic regenerative capacity declines with age despite the presence of resident progenitors, and they highlight the need for strategies that address both loss of functional epithelium and the accumulation of inhibitory niches [14, 16–19, 23, 36, 38, 39].

Viewed within the broader framework of aging biology, thymic involution thus emerges not as an isolated organ-level event but as a convergence point for multiple hallmarks of aging. Epigenetic silencing of FOXN1 links thymic decline to the aging epigenome; telomere attrition in TECs limits regenerative reserve; mitochondrial dysfunction and altered NAD⁺ metabolism in stromal cells contribute to adipogenic conversion; and the SASP of senescent cells accumulating within and around

the thymus feeds back to further disrupt the epithelial niche [8–10, 14, 15, 23, 54]. Systemic metabolic signals—declining growth hormone, IGF-1, and FGF21; rising sex steroids and cortisol; chronic hyperglycemia and dyslipidemia—further modulate thymic stromal viability through pathways that intersect with those governing metabolic aging in other tissues [9, 15, 19, 23, 42]. This convergence positions the thymus as both a sensor and an effector of organismal aging: its involution reflects systemic aging processes, while its functional decline in turn amplifies immunosenescence, inflammaging, impaired senescent-cell clearance, and downstream disease. Recognizing this bidirectional relationship has implications for therapeutic strategy, as it suggests that thymus-directed interventions may be most effective when combined with approaches that address the systemic metabolic and inflammatory milieu rather than targeting the organ in isolation [3, 5, 8–10, 23] (Fig. 1).

Endogenous regenerative capacity and epithelial stem cells

Despite progressive involution, the adult thymus retains significant endogenous regenerative capacity. In mice, acute insults such as chemotherapy, irradiation, or sepsis



AIRE, autoimmune regulator; cTEC/mTEC, cortical/medullary TEC; EMT, epithelial–mesenchymal transition; RTE, recent thymic emigrant; SASP, senescence-associated secretory phenotype; TREC, T-cell receptor excision circle.

Fig. 1 Mechanistic cascade of thymic involution and nodes of therapeutic intervention. Age-related thymic involution arises from converging upstream drivers: systemic signals (rising sex steroids; declining somatotrophic axis [GH, IGF-1, ghrelin]; falling FGF21 and altered NAD⁺ metabolism; inflammaging and the senescence-associated secretory phenotype) and local, cell-intrinsic signals (FOXN1 promoter methylation; PPAR γ /u03B2 activation downstream of xanthine oxidoreductase; Wnt4 loss with LAP2/u03B1 gain; TGF- β /u03B2 activation; telomere attrition). These produce intrinsic thymic epithelial cell (TEC) degeneration\u2014loss of FOXN1-dependent TEC identity, adipogenic conversion via epithelial-to-mesenchymal transition (FoxC2, FSP-1), fibrosis, accumulation of atypical TECs that sequester trophic factors such as BMP4, and decline in cortical and medullary TEC function and AIRE-dependent central tolerance\u2014which in turn yields the downstream immunosenescence phenotypes (reduced naive T-cell output, contracted T-cell receptor repertoire, impaired negative selection) and their clinical sequelae (infection susceptibility and vaccine failure, increased cancer incidence, late-onset autoimmunity, and impaired post-treatment or HIV immune reconstitution). The IL-22 \u2013 STAT3 \u2013 FOXN1 axis (center) is the principal endogenous regenerative cascade and a key intervention target. Therapeutic modalities (lower panel, dashed arrows) are mapped to their predominant site of action: sex-steroid ablation, somatotrophic modulation, senolytics, and metabolic modulators act on upstream drivers; FGF21, IL-22/STAT3 agonism, KGF (FGF7)/BMP4, and FOXN1 gene therapy or reprogramming act on the degenerating epithelium; and IL-7 acts peripherally, expanding mature T cells with limited restoration of de novo thymopoiesis. AIRE, autoimmune regulator; cTEC/mTEC, cortical/medullary thymic epithelial cell; EMT, epithelial-to-mesenchymal transition; RTE, recent thymic emigrant; SASP, senescence-associated secretory phenotype; TCR, T-cell receptor; TEC, thymic epithelial cell; TREC, T-cell receptor excision circle

are followed by partial recovery of thymic architecture and output, a process driven by coordinated responses of epithelial cells, endothelial cells, and mesenchymal stromal cells [16–19, 36–39]. Endogenous cytokines, including IL-22 produced by innate lymphoid and Th17 cells, and endothelial-derived BMP4, play pivotal roles by promoting epithelial survival, proliferation, and upregulation of key genes such as FOXP1 and DLL4 [14, 16–19, 36, 38, 39].

In humans, the identification of thymic epithelial stem cells has substantially altered the conceptual landscape. Polykeratin-positive epithelial stem cells with pleiotropic multilineage potential have been discovered in the postnatal thymus, residing in subcapsular and perivascular niches and capable of giving rise to the full spectrum of cortical and medullary epithelial subsets [16, 22]. These cells self-renew extensively *in vitro*, maintain clonogenicity, and can reconstitute complex thymic epithelial architecture when transplanted onto decellularized scaffolds [15, 16, 22]. Complementary work has shown that postnatal human stromal progenitor cells can regenerate functional thymic tissue *in vivo*, supporting T-cell development and central tolerance [15, 16, 22].

Collectively, these data indicate that the involuted thymus retains a resident epithelial stem-cell compartment and latent regenerative programs that can be reactivated, at least under experimental conditions [14–19, 22, 30]. However, the presence of age-associated epithelial defects, altered stromal–immune interactions, and systemic inhibitory signals means that endogenous regeneration in older adults is often incomplete and may be maladaptive in certain contexts [14, 16–19, 23, 36, 38, 39]. This duality—the coexistence of stemness and structural degeneration—underpins what has been termed the “thymus regeneration paradox” and has important implications for therapeutic strategies that seek to harness or augment regenerative capacity [14, 16–19, 23].

Human evidence for thymic relevance in adulthood

Thymic health, mortality, and disease incidence

For decades, the clinical significance of the adult thymus was underestimated, largely because of its radiographic invisibility and the assumption that peripheral mechanisms compensate for declining thymic output [1–3, 5, 7, 11, 12]. This view has been challenged by recent large-scale imaging studies that use AI-assisted analysis of routine chest CT scans to derive quantitative thymic health scores in asymptomatic adults [11, 20–22]. In these cohorts, higher thymic health was associated with substantially lower all-cause mortality and reduced incidence of lung cancer and cardiovascular disease, independent of age, sex, smoking status, prior disease, and conventional risk factors [9, 11–13, 20–22]. Thymic health also correlated with systemic inflammatory and

metabolic markers and with modifiable lifestyle factors, suggesting that thymic decay is both a marker and potential mediator of broader age-related pathophysiology [8, 9, 11–13, 20–22].

Important caveats apply to the interpretation of these observational associations. Thymic fat fraction on CT is influenced by body composition, metabolic health, smoking history, prior thoracic radiation or chemotherapy, and general frailty—all of which are themselves associated with mortality and disease incidence independently of thymic function [8, 9, 11, 21, 22]. The extent to which radiographic thymic health reflects *de novo* thymopoietic capacity, as opposed to serving as an integrative biomarker of systemic metabolic and inflammatory status, remains to be established. Although the imaging studies adjusted for major confounders, residual confounding cannot be excluded, and it would be premature to interpret these associations as evidence that thymic involution directly causes the observed outcomes. Prospective studies incorporating functional thymic readouts (TREC_s, recent thymic emigrants, TCR repertoire diversity) alongside imaging will be needed to disentangle the independent contribution of thymic function from correlated systemic aging processes.

Complementary observational data from solid organ transplantation and iatrogenic immunosuppression underscore the importance of intact T-cell immunity in cancer and infection risk. Transplant recipients on long-term immunosuppressive regimens have a two- to four-fold increased overall cancer risk with certain virus-associated and epithelial cancers, elevated up to 10–100-fold, and they experience substantial infection-related morbidity [9, 12, 13, 24, 25]. These findings, together with similar patterns in HIV infection and primary immunodeficiencies, are consistent with the immunological model of carcinogenesis in which declining T-cell production and surveillance, rather than mutation accumulation alone, may account for a substantial fraction of the age-related rise in cancer incidence [9, 11–13, 20, 24–27]. Mathematical modeling supports this view, showing that the exponential decline in thymic output with a half-life of approximately 16 years can quantitatively reproduce incidence curves across diverse tumor types, although the model does not exclude contributions from mutation accumulation, epigenetic drift, or other hallmarks of aging [11].

Thymectomy and adult immune competence

Adult thymectomy has historically been considered clinically benign outside of specific contexts such as myasthenia gravis, in part because peripheral T-cell pools in younger adults initially appear preserved [1–3, 7]. A recent large New England Journal of Medicine study has challenged this assumption by following adults who

underwent thymectomy for non-malignant indications and comparing them with matched controls [1, 21, 22]. Thymectomised individuals exhibited modest but significant reductions in total, CD4⁺, and naïve T-cell counts, particularly in the early years after surgery, and they showed higher long-term risks of mortality, cancer, and autoimmune disease [1, 6, 11–13, 21, 22]. Compensatory mechanisms, including increased peripheral T-cell proliferation and elevated IL-7 levels, partially maintained lymphocyte numbers but did not restore naïve T-cell generation or TCR diversity [4, 5, 9, 11, 13, 21, 22, 24, 25, 33]. Notably, the relatively mild phenotype of adults thymectomised in youth reflects robust peripheral homeostatic compensation rather than dispensability of the thymus. In the absence of ongoing thymic output, naïve T cells are maintained in situ within lymphoid tissues through low-level self-renewal and memory-compartment remodeling, which preserves peripheral cell numbers while masking the underlying decline in recent thymic emigrants [55]. The principal long-term consequence of this compensation is therefore a gradual erosion of naïve repertoire diversity rather than an acute immunological collapse; consistent with this, individuals thymectomised in early childhood develop an oligoclonal, memory-skewed T-cell compartment and, in a subset, a prematurely aged immune-risk phenotype driven by cytomegalovirus, indicating that homeostatic compensation is partial and ultimately finite [56].

Additional observational work in specific disease populations supports a continuing role for thymic function in adulthood. In HIV infection, thymic damage from direct viral cytotoxicity, progenitor cell depletion, inflammatory destruction of epithelial architecture, and fibrosis leads to profound and often irreversible loss of thymic output [5, 6, 9, 13, 26, 27]. Even with effective antiretroviral therapy, a substantial fraction of patients remain immunological non-responders with persistently low CD4⁺ counts, reduced naïve T cells, and increased morbidity and mortality, reflecting a structural failure of thymic regeneration [6, 9, 13, 26, 27]. Similar patterns of impaired thymic recovery and incomplete immune reconstitution are observed after intensive chemotherapy and hematopoietic stem-cell transplantation, where poor thymic output predicts infectious complications, chronic graft-versus-host disease, and inferior survival [16–19, 23, 28, 36–39].

Infection, vaccination, and pandemic vulnerability

Epidemiological data demonstrate that older adults experience disproportionately high morbidity and mortality from common infections such as influenza, pneumonia, and sepsis, as well as poorer responses to vaccination [3, 5, 9, 23–25, 45, 46]. Reduced naïve T-cell numbers and restricted TCR diversity limit the ability to mount effective responses to novel or antigenically drifted pathogens,

contributing to vaccine failure and severe disease [4, 5, 11, 24, 25, 45, 46]. Quantitative reviews show that influenza vaccine efficacy in adults over 65 is substantially lower than in younger adults, and similar age gradients are seen for pneumococcal and varicella-zoster vaccines [24, 25].

The COVID-19 pandemic provided a stark natural experiment. Age-specific infection fatality curves for SARS-CoV-2 closely mirrored the trajectory of thymic involution, with very low mortality in children and young adults and an exponential increase after approximately 50 years of age [5, 11, 57]. Immunological follow-up studies indicate that many individuals with persistent post-acute sequelae exhibit features of T-cell dysfunction, contracted TCR repertoire, and altered cytokine profiles months after infection [45, 46]. Although multiple factors contribute to these patterns, the alignment between thymic decline, immunosenescence, and pandemic vulnerability strengthens the rationale for thymus-focused interventions as one component of strategies to enhance population resilience to emerging pathogens [3, 5, 8, 9, 11, 23, 45, 46]. Importantly, the relationship between SARS-CoV-2 and the thymus is not solely epidemiological. The virus directly targets the thymic microenvironment: angiotensin-converting enzyme 2, the principal entry receptor, is expressed by thymic epithelium and in particular by medullary thymic epithelial cells, and infection downregulates epithelial adhesion and survival programs, with measurable reductions in thymic output (TRECs) that correlate inversely with disease severity in patients [58]. In humanized ACE2 mouse models, SARS-CoV-2 infects thymocytes and drives interferon- γ -dependent thymic atrophy with depletion of double-positive cells and contraction of the peripheral TCR repertoire [59]. These data establish a bidirectional mechanism in which acute viral injury to the thymus is superimposed on pre-existing age-related involution. This consideration tempers any inference that thymic restoration alone would resolve post-acute sequelae such as long COVID, since it implies that virus-mediated thymic damage and host immunosenescence are compounding rather than independent contributors.

Autoimmunity, cardiovascular disease, neurodegeneration, and frailty

The epidemiology of autoimmunity, cardiovascular disease, neurodegenerative disorders, and frailty suggests that these conditions share common immunological and inflammatory underpinnings that may be influenced by thymic status. Late-onset autoimmune diseases, including giant cell arteritis, polymyalgia rheumatica, and certain forms of rheumatoid arthritis and autoimmune thyroiditis, peak in incidence decades after substantial thymic involution, consistent with impaired negative

selection and reduced Treg generation [3, 5, 6, 23, 47]. Experimental models confirm that thymic involution perturbs central tolerance and allows autoreactive clones to escape deletion, promoting chronic inflammation [3, 5, 6, 9, 23, 47].

In cardiovascular disease, clonal hematopoiesis of indeterminate potential, particularly involving TET2 and DNMT3A mutations, drives pro-inflammatory monocyte and macrophage phenotypes that accelerate atherosclerosis, while senescent vascular cells contribute to plaque instability via the senescence-associated secretory phenotype [9, 13, 43, 54]. Thymic decline may exacerbate these processes by reducing Treg-mediated control of vascular inflammation and impairing clearance of senescent cells [6, 8, 9, 13, 43, 54]. Neurodegenerative diseases such as Alzheimer's disease exhibit prominent microglial activation and neuroinflammation, and preclinical data indicate that enhancing adaptive immunity can modulate microglial function and improve clearance of pathological aggregates [9, 10, 29]. Finally, frailty, sarcopenia, and osteoporosis are increasingly recognized as downstream manifestations of chronic inflammation, immunosenescence, and impaired tissue homeostasis, all of which may be influenced by thymic function [3, 5, 6, 8–10, 23].

Together, these human data reposition the thymus as a clinically relevant organ in adulthood whose structural and functional status is associated with a broad range of health outcomes [1–3, 5–7, 9, 11–13, 20–25, 28, 29]. They do not by themselves prove that thymus-targeted interventions will prevent or reverse these conditions, but they provide a strong empirical and mechanistic foundation for considering thymic restoration as a potential upstream strategy to mitigate immunosenescence and its clinical sequelae [2, 3, 5–9, 11–13, 20–25, 28, 29].

Because these associations are predominantly observational, translating them into a rationale for intervention requires an explicit inferential chain rather than a single leap from correlation to therapy. First, the epidemiological links between reduced thymic output or radiographic involution and adverse outcomes establish that thymic status is a marker of risk. Second, several lines of evidence advance this toward causal inference: thymectomy cohorts constitute a quasi-experimental loss-of-function manipulation in humans; HIV and post-transplant settings show that the degree of thymic impairment tracks with immune-reconstitution failure in a graded fashion; and mechanistic work supplies a coherent pathway connecting diminished naïve output and constrained TCR diversity to impaired immunosurveillance and tolerance. Third, causal plausibility justifies thymus-directed targeting only if the thymus is a tractable upstream node whose restoration could realistically alter downstream outcomes—a premise supported by the persistence of epithelial progenitors and inducible regenerative pathways

described earlier. It is this progression—from risk marker, to probable causal contributor, to modifiable upstream target—rather than any individual correlation, that motivates the domain-specific evaluation below. Accordingly, the tiers that follow grade not only the strength of association but the completeness of this inferential chain for each indication.

Therapeutic domains and evidence tiers

Multiple lines of evidence now link thymic status to clinically important outcomes across several domains, but the strength and nature of support differ substantially between indications [1–3, 5–9, 11–13, 20–25, 28, 29]. For clarity, these domains can be provisionally tiered into: (i) established or higher-confidence indications where human data and mechanistic plausibility align; (ii) high-plausibility indications with strong mechanistic and circumstantial support but limited direct intervention data; and (iii) emerging or speculative indications where thymic restoration is conceptually attractive but largely untested (Table 1).

Among the established (Tier 1) domains, three stand out. First, cancer immunosurveillance: modeling work suggests that age-related declines in thymic output and T-cell production can quantitatively account for a substantial fraction of the rise in cancer incidence with age, and observational data from transplant and HIV cohorts demonstrate that sustained T-cell impairment greatly increases cancer risk [5, 9, 11–13, 20, 24–27]. Second, infectious disease vulnerability and vaccine responsiveness: older adults with involuted thymi exhibit reduced naïve T cells, impaired responses to common vaccines, and disproportionate morbidity and mortality from pathogens such as influenza and SARS-CoV-2 [3, 5, 9, 11, 23–25, 45, 46, 57]. Third, post-treatment immune reconstitution: after chemotherapy, hematopoietic stem-cell transplantation, or HIV, incomplete thymic recovery is associated with persistent lymphopenia, infection, chronic graft-versus-host disease, and excess mortality [5, 6, 9, 13, 16–19, 23, 26–28, 36–39].

High-plausibility (Tier 2) domains are those where thymic function is tightly intertwined with disease mechanisms but direct evidence from thymus-targeted interventions remains limited. Autoimmune disease is a prominent example: thymic involution perturbs negative selection and Treg output, late-onset autoimmunity emerges in the decades after substantial thymic decline, and experimental models show that restoring thymic tolerance mechanisms can reduce autoimmune pathology. Chronic herpesvirus control and HIV immunological non-response also fall into this category, as both involve persistent antigenic stress, T-cell exhaustion, and structural thymic damage that limits de novo T-cell generation [3, 5, 6, 9, 13, 23–27]. Post-acute infection syndromes

Table 1 Summary of clinical domains for thymic restoration, classified by evidence tier, with key supporting evidence and proposed biomarker endpoints

Clinical Domain	Evidence Tier	Key Supporting Evidence	Proposed Biomarker Endpoints
Cancer immunosurveillance	Established	Thymic involution–cancer incidence modeling [11]; transplant cancer risk [12]; thymectomy outcomes [21]	Naïve T-cell counts; TCR diversity; cancer incidence
Infectious disease vulnerability/vaccine responsiveness	Established	Influenza vaccine efficacy decline [24]; COVID-19 age–mortality gradient [57]; TCR contraction [4]	Vaccine seroconversion; infection rates; TREC levels
Post-treatment immune reconstitution	Established	HSCT thymic recovery [28, 36–38]; HIV immunological non-response [26, 27]; cGVHD prevention by IL-22 [37]	CD4 + recovery kinetics; TREC; recent thymic emigrants; cGVHD incidence
Autoimmune disease	High-plausibility	Thymic involution perturbs negative selection [6]; late-onset autoimmunity epidemiology [3, 5]	Treg frequency; autoantibody titres; disease flare rates
HIV immunological non-response	High-plausibility	Thymic damage from HIV [26]; persistent low CD4 + despite ART [27]; structural thymic failure [5]	CD4 + count trajectory; TREC; naïve/memory T-cell ratio
Post-acute infection syndromes (long COVID)	High-plausibility	Persistent T-cell dysfunction post-SARS-CoV-2 [45]; contracted TCR repertoire [46]	T-cell subsets; TCR diversity; symptom resolution
Neurodegeneration	Speculative	Adaptive immunity modulates microglial function [29]; neuroinflammation–aging link [9, 10]	Peripheral immune phenotyping; neuroinflammatory biomarkers
Cardiovascular disease	Speculative	CHIP and vascular inflammation [13]; Treg-mediated atheroprotection [9]; SASP in plaque instability [54]	Treg counts; hsCRP/IL-6; MACE endpoints
Frailty/sarcopenia/musculoskeletal aging	Speculative	Inflammaging and tissue homeostasis [8, 9]; immunosenescence–frailty association [3, 5]	Frailty index; grip strength; inflammatory markers

such as long COVID may represent a composite domain in which impaired thymic output interacts with mitochondrial dysfunction, autonomic and endothelial dysregulation, and neuroinflammation, although thymus-directed interventions have not yet been tested [3, 6, 9, 10, 13, 23, 29, 45, 46].

More speculative (Tier 3) domains include neurodegeneration, cardiovascular disease, frailty and musculoskeletal aging, and mitochondrial disorders. In Alzheimer's disease and related conditions, experimental enhancement of adaptive immunity can modulate microglial function and promote clearance of pathological aggregates, but the specific contribution of thymic restoration remains uncertain. In atherosclerosis, clonal hematopoiesis and inflammaging create a pro-inflammatory milieu that might be mitigated by improved thymic output and Treg-mediated regulation, yet this concept is largely extrapolated from mechanistic work. Frailty, sarcopenia, osteoporosis, and mitochondrial dysfunction are all influenced by chronic inflammation and immune–metabolic crosstalk, so thymic restoration could theoretically contribute to improved healthspan, particularly in combination with other interventions. For these emerging domains, thymus-focused strategies should be viewed as hypothesis-generating rather than evidence-based interventions at present.

Current and emerging thymus-targeted approaches

Hormonal and somatotrophic modulation

Hormonal manipulation was among the earliest approaches to thymus rejuvenation. Androgen deprivation in mice and humans can induce thymic regrowth

and increase thymocyte numbers, reflecting the well-documented inhibitory effects of sex steroids on thymic epithelial proliferation and thymopoiesis [3, 19, 32, 53]. Castration or pharmacological androgen blockade in animal models leads to enlargement of the thymus and increased export of naïve T cells, although the durability and functional impact of these changes in humans remain incompletely characterized [32, 42, 53]. Modulation of the somatotrophic axis, particularly through growth hormone and ghrelin, has also been shown to influence thymic size and function in preclinical studies, likely through direct effects on thymic stromal cells and indirect effects on systemic metabolism [19, 42].

The TRIIM trial represents a notable human proof-of-concept [31]. In this small, uncontrolled study, middle-aged and older men received a combination of recombinant growth hormone, metformin, and DHEA for one year, resulting in MRI-detected changes in thymic tissue, increased markers of naïve T cells, and an apparent reversal of some epigenetic aging signatures [31]. While these findings are intriguing, the study's size, design, and composite intervention make it difficult to attribute effects specifically to thymic mechanisms or to generalize to broader populations. More broadly, endocrine interventions carry risks of metabolic, neoplastic, and cardiovascular side effects, and their risk–benefit profile for thymus-directed indications will need to be established in controlled, context-specific trials [19, 31, 42, 53].

Cytokines and growth factors

Cytokine and growth-factor therapies seek to exploit endogenous regenerative pathways identified in

preclinical work. IL-22 is a key example: it is produced by innate lymphoid and Th17 cells after thymic injury, signals through STAT3 to promote thymic epithelial survival and proliferation and has been shown to accelerate thymic recovery and reduce chronic graft-versus-host disease in murine transplantation models [36, 37]. Keratinocyte growth factor (KGF, FGF7), acting via FGFR2IIIb on thymic epithelial cells, enhances post-injury thymopoiesis and supports thymic microenvironment integrity, while endothelial-derived BMP4 further boosts FOXP1 expression and downstream Notch ligand signaling [16–19, 34, 38, 39, 44]. FGF21 has recently emerged as a stromal-derived modulator that delays thymic aging, reduces adipogenic replacement, and upregulates key trophic factors, providing a mechanistic link between metabolic state and thymic health [15].

IL-7 occupies a special position because of its dual roles in thymopoiesis and peripheral T-cell homeostasis [33]. Clinical studies of IL-7 in lymphopenic patients have demonstrated robust peripheral T-cell expansion but have generally failed to show corresponding increases in markers of thymic output, such as TCR excision circles or recent thymic emigrants, suggesting that peripheral effects predominate in adult humans [33]. This pattern is well illustrated in HIV infection: in antiretroviral-treated patients with incomplete CD4 recovery, recombinant human IL-7 (CYT107) produced brisk, dose-dependent expansion of predominantly naïve and central-memory CD4 T cells, with only modest and variable increases in thymic output and TCR-repertoire breadth, and the expanded cells did not exhibit a regulatory or activated phenotype [60]. This pattern was established in the first-in-human study of recombinant human IL-7, in which expansion was driven preferentially by naïve subsets and recent thymic emigrants, broadening TCR-repertoire diversity, while the proportions of regulatory T cells and senescent effector cells declined [61]. In subsequent phase II trials of repeated dosing (INSPIRE 2 and 3), sustained CD4 restoration above 500 cells/ μ L was achievable in most participants, but anti-IL-7 binding antibodies developed in the large majority and neutralizing antibodies in roughly one-third, indicating that immunogenicity is a principal constraint on repeated administration [62]. Across indications, the dominant effect of IL-7 in adults is thus peripheral homeostatic expansion rather than restoration of *de novo* thymopoiesis, a distinction that should be weighed when positioning IL-7 within thymus-directed strategies. Similarly, a clinical trial of palifermin (recombinant KGF) in humans unexpectedly impaired naïve T-cell recovery in some settings, highlighting that extrapolation from preclinical models can be misleading [34, 38, 39, 43]. These experiences underscore that cytokine and growth-factor therapies must be evaluated carefully in disease- and age-specific contexts, with attention

to dose, timing, and combined effects on thymic stromal cells and peripheral lymphocyte subsets [16–19, 33, 34, 36–39, 43, 44].

Cell-based and tissue-engineering strategies

Advances in thymic epithelial stem-cell biology have opened new avenues for cell-based and tissue-engineering approaches. Polykeratin-positive epithelial stem cells identified in the human postnatal thymus reside in discrete niches, exhibit extensive self-renewal, and can differentiate into the full spectrum of cortical and medullary epithelial subtypes, including AIRE-expressing medullary cells and specialized cortical subsets [16, 22]. These cells can be expanded *in vitro* and, when seeded onto appropriate scaffolds, self-organize into structures that recapitulate key features of thymic architecture and support thymopoiesis in experimental systems [15, 16, 22]. Parallel work has shown that postnatal human stromal progenitors can reconstitute functional thymic tissue *in vivo*, further supporting the feasibility of tissue-engineered thymic grafts [15, 16, 22].

In mice, forced expression of FOXP1 in fibroblasts or other stromal cells can reprogram them into thymic epithelial-like cells capable of supporting thymocyte development when transplanted intrathymically, leading to structural and functional rejuvenation of the aged thymus [14, 17, 30, 35]. These findings suggest that a combination of gene-modified stromal cells and supportive scaffolds could be used to repair or augment damaged thymic tissue in humans, particularly in settings of profound thymic destruction such as congenital athymia, severe HIV-related damage, or intensive chemotherapy. However, scaling such approaches to human organs, ensuring appropriate vascularization and integration with host hematopoiesis, and managing alloimmune responses remain substantial challenges [14–17, 22, 30, 35].

Gene-therapy concepts

Gene-therapy strategies for thymic regeneration build on preclinical demonstrations that targeted gene delivery to thymic epithelial cells can restore architecture and function in monogenic immunodeficiency models [40]. Intrathymic AAV-based gene transfer in mice has successfully corrected selected immunodeficiencies by restoring expression of critical signaling molecules, rapidly re-establishing medullary organization and AIRE-expressing cells, and producing durable T-cell reconstitution [40]. Conceptually, more complex constructs could combine transcriptional regulators such as FOXP1, tolerance-related factors such as AIRE, chemokines such as CCL25 to recruit progenitors, and stromal-support factors including FGF21 or telomerase components to combat fibrosis and epithelial senescence [14, 15, 17, 31, 35, 37, 39–41]. In humans, systemic AAV-mediated hTERT gene

Table 2 Translational roadmap: thymus-directed intervention classes, target mechanisms, candidate populations, proposed biomarker and clinical endpoints, and principal safety liabilities

Intervention Class	Primary Mechanism	Candidate Population	Biomarker Endpoints	Clinical Endpoints	Key Safety Liabilities
Hormonal/somato-tropic (GnRH agonists, GH, ghrelin, DHEA)	Sex steroid ablation; somatotrophic axis activation of TEC proliferation	Healthy older adults (> 60 yr); post-menopausal women	MRI thymic volume; TREC; naïve T-cell counts; epigenetic clocks	Vaccine seroconversion; infection incidence	Metabolic/CV effects of GH; cancer promotion (IGF-1); bone loss with GnRH
Cytokine/growth factor (IL-22, IL-7, KGF/BMP4, FGF21)	TEC survival (STAT3/Mcl-1); FOXP1 upregulation; stromal trophic support	Post-HSCT; post-chemotherapy lymphopenia; HIV INRs	TREC; RTE; CD4 + reconstitution kinetics; TCR diversity	cGVHD incidence; infection-free survival; CD4 + recovery	Peripheral T-cell expansion without thymopoiesis (IL-7); impaired naïve recovery (KGF in humans); autoimmunity
Cell-based/tissue engineering (TEPCs, FOXP1-reprogrammed fibroblasts, organoids)	Epithelial scaffold reconstitution; de novo thymopoietic niche formation	Congenital athymia; severe post-HIV/HSCT thymic destruction	Naïve T-cell output; TCR diversity; AIRE expression in graft	Infection-free survival; autoimmune disease incidence	Alloimmune rejection; graft vascularisation failure; disordered T-cell selection; scale-up feasibility
Gene therapy (intra-thymic AAV delivery of FOXP1, AIRE, CCL25, FGF21, hTERT)	Multi-pathway TEC reprogramming; progenitor recruitment; anti-fibrotic/anti-senescence	Monogenic immunodeficiencies (near-term); severe structural thymic damage; age-related involution (longer-term)	Transgene expression (biopsy); TREC; RTE; TCR diversity; thymic imaging	Immune reconstitution; infection/cancer incidence	Pre-existing AAV NABs; ectopic expression; insertional mutagenesis; oncogenicity (hTERT); autoimmunity from tolerance disruption

Abbreviations: cGVHD chronic graft-versus-host disease, CV cardiovascular, GH growth hormone, GnRH gonadotrophin-releasing hormone, HSCT hematopoietic stem-cell transplantation, INR immunological non-responder, NABs neutralizing antibodies, RTE recent thymic emigrant, TEPC thymic epithelial progenitor cell
See text for references

transfer has been reported in a single long-term case, with progressive leukocyte telomere lengthening over a 5.8-year follow-up and no attributed adverse events, providing preliminary evidence that telomerase-directed gene transfer is feasible, although such anecdotal data require controlled validation [63].

Such approaches offer the potential to address multiple bottlenecks of thymic involution simultaneously—rebuilding epithelial architecture, enhancing progenitor recruitment and thymocyte survival, restoring central tolerance, and limiting fibrotic or adipogenic replacement [14, 15, 17, 31, 35, 37, 39–41]. However, they also pose significant translational challenges. Efficient and specific targeting of thymic epithelial cells in older humans, pre-existing neutralizing antibodies to AAV vectors, the risk of ectopic expression in hematopoietic or non-target tissues, and long-term safety concerns related to oncogenicity and autoimmunity will all require careful preclinical and clinical evaluation [6, 9, 10, 13, 15, 37, 40, 41, 43, 54]. Given these complexities, thymic gene therapy is likely to progress initially in narrowly defined indications—such as severe structural thymic damage or specific immunodeficiencies—before broader applications to age-related immunosenescence can be contemplated [15, 37, 40, 41]. The key features, target populations, biomarker endpoints, and safety liabilities of each intervention class are summarized in Table 2.

Limitations, risks, and open questions

Despite substantial progress, several limitations and open questions temper the current enthusiasm for thymus-targeted therapies. First, the causal contribution of thymic restoration to clinically meaningful endpoints remains unproven in most domains. Observational associations between thymic health, mortality, and disease incidence, and small interventional studies such as TRIIM, provide important signals but cannot substitute for randomized, adequately powered trials [5, 6, 9, 11–13, 20–22, 24, 25, 28, 29, 31, 42, 45, 46, 53]. The extent to which improvements in thymic structure and surrogate immunological markers translate into reductions in infection, cancer, autoimmune flares, or frailty is unknown, and may differ substantially between indications and patient populations.

Second, the structural and cellular context of the aged thymus may limit the efficacy of pro-regenerative interventions. Age-associated atypical epithelial cells, fibrosis, adipogenic replacement, and vascular changes all create a microenvironment in which progenitors and regenerative signals may be sequestered or rendered ineffective [14, 16–19, 23, 36, 38, 39]. In such settings, simply providing additional growth factors or transcriptional activators may be insufficient or could produce disorganized or dysfunctional tissue. Determining when endogenous regeneration is still tractable, and when more

radical tissue-engineering or replacement strategies are required, will be critical for rational patient selection.

Third, safety considerations are particularly important for thymus-directed therapies, especially in older adults with comorbidities. Overzealous thymic stimulation could theoretically promote autoimmunity by expanding self-reactive clones or disrupting established tolerance, particularly if AIRE expression or negative selection remain impaired [5, 6, 9, 10, 13–15, 28, 33–41, 43, 54]. In this respect, the quality of medullary thymic epithelial cell (mTEC) function is as consequential as the quantity of thymic output: because mTECs mediate promiscuous self-antigen expression and AIRE-dependent negative selection, interventions that increase thymopoiesis without commensurately restoring competent medullary education could export inadequately tolerized, potentially autoreactive T cells and thereby provoke rather than prevent autoimmunity. Strategies that rebuild epithelial architecture should therefore be assessed for restoration of central tolerance, not merely naïve-cell output. Thymic expansion might also interact with clonal hematopoiesis, senescent cell burden, or latent infections in unpredictable ways [6, 9, 10, 13, 43, 54]. Past experiences with IL-7 and KGF illustrate that interventions with apparently favorable preclinical profiles can have unexpected effects on human T-cell dynamics, including skewing toward peripheral expansion rather than *de novo* thymopoiesis or impairing naïve T-cell recovery [33, 34, 36–39, 43]. Gene-therapy approaches add additional layers of risk related to insertional mutagenesis, ectopic expression, delayed immune responses to vector or transgene products, and long-term effects of telomerase or other mitogenic factors [15, 37, 40, 41].

A further consideration is conceptual rather than technical. This review has treated thymic involution principally as a contributor to age-related pathology, but an influential alternative view holds that involution is, at least in part, an evolved adaptation rather than a simple degenerative failure [64]. On this account, progressive restriction of thymic output may reduce the cumulative risk of generating autoreactive clones and conserve the considerable metabolic cost of maintaining a large, active thymus once the primary T-cell repertoire has been established. If correct to any meaningful degree, this protective framing carries two implications. First, wholesale, non-selective reversal of involution could reintroduce the very liabilities—autoreactivity and metabolic burden—that involution may serve to limit, reinforcing the tolerance-focused safety considerations noted above. Second, the therapeutic objective may be better defined as restoring sufficient, well-regulated thymic function in defined high-risk contexts rather than maximally rejuvenating the organ in all adults. We therefore frame thymic restoration as a context-dependent opportunity while

acknowledging that the adaptive value of involution remains an open and consequential question, and that the balance of benefit and harm is likely to differ markedly across the evidence tiers proposed here.

Finally, thymus-directed strategies must be integrated conceptually and practically into broader frameworks of aging and disease modification. Thymic involution is tightly linked to systemic processes such as inflammaging, metabolic dysregulation, clonal hematopoiesis, and mitochondrial dysfunction, and it is unlikely that restoring thymic output alone will reverse established pathology across all affected organs [3, 5, 6, 8–10, 13, 23]. Identifying which patient groups and disease stages are most likely to benefit from thymic restoration, establishing appropriate combinations with other interventions (for example senolytics, metabolic modulators, or anti-inflammatory therapies), and defining realistic goals—such as reduced infection burden or improved vaccine responses rather than complete disease reversal—will be essential. Addressing these questions through carefully designed mechanistic studies and clinical trials will determine whether thymus regeneration can transition from a compelling theoretical construct to a practical tool for extending immune healthspan and reducing the burden of age-related disease.

Discussion

The evidence reviewed here supports a coherent but still incomplete case. Convergent human data from thymectomy cohorts, large radiographic studies, transplant populations, and HIV infection establish the adult thymus as a clinically relevant organ whose loss or functional failure carries measurable long-term cost, justifying its treatment as a legitimate therapeutic target rather than a vestigial remnant [1, 5, 6, 9, 11–13, 21, 22, 24–28]. Yet the same body of evidence is internally tensioned, and the task here is to reconcile those tensions rather than restate the mechanisms detailed above.

Three tensions structure the field. First, a preclinical–clinical gap: interventions that robustly regenerate the rodent thymus—enforced FOXP1 expression, IL-22, endothelial BMP4—have translated inconsistently to humans, where IL-7 produces peripheral T-cell expansion rather than restored thymopoiesis and palifermin has paradoxically impaired naïve recovery in some settings [33, 34, 36–39, 44, 60, 62]. Second, a latent-capacity-versus-inhibitory-niche tension: human thymic epithelial progenitors persist into adulthood, yet age-associated atypical epithelial cells, fibrosis, and PPAR γ - and Wnt4/LAP2 α -driven adipogenic conversion create a microenvironment that actively sequesters pro-regenerative signals [14, 36, 38, 39, 48, 51]. Retained progenitor potential is therefore necessary but not sufficient for regeneration. Third, species- and context-specificity:

regenerative programs differ across vertebrates, cautioning against direct extrapolation from mouse or axolotl to aged humans [16–19, 53].

These tensions converge on a specific caution regarding FOXN1-centric strategies. FOXN1 re-expression is sufficient to rejuvenate the young or genetically defined thymus and remains a logical anchor for any regenerative construct, but in the aged human thymus it is unlikely to be sufficient alone. It acts within a degraded niche in which growth-factor sinks, fibrosis, adipogenic stroma, and vascular change blunt epithelial responses; restoring the quantity of output without restoring medullary AIRE-dependent negative selection risks exporting inadequately tolerized cells; local adipogenic drivers operate in parallel and are not corrected by FOXN1 alone [48, 51]; and the systemic milieu of inflammaging and metabolic dysregulation constrains stromal viability independently of epithelial identity. Effective restoration will therefore require multi-nodal strategies that simultaneously re-establish epithelial identity, dismantle inhibitory niches, restore tolerance competence, and address the systemic environment (Fig. 1).

A dialectical reading further requires holding the protective hypothesis alongside the pathology framing: if involution is in part an evolved adaptation, the therapeutic objective becomes regulated sufficiency in defined high-risk contexts rather than maximal rejuvenation [64]. This reframing aligns the goal of intervention with its principal safety constraint and with the evidence tiers proposed here.

Taken together, the strongest human signals remain observational or derive from small, uncontrolled studies; causal inference will require randomized trials powered for domain-specific endpoints, such as infection rates in older adults, immune reconstitution in transplant and HIV immunological non-responders, or defined composite endpoints in cancer prevention [5, 9, 11–13, 20–22, 24–29, 45, 46]. Given the heterogeneity of thymic damage and downstream disease, no single uniform intervention is likely to succeed; thymus-directed therapy is best positioned within a combinatorial, indication-specific portfolio alongside senolytics, metabolic modulators, structured exercise, and immune-cell engineering [3, 8–10, 23, 54]. The near-term task of the field is thus less to identify a definitive intervention than to build the rational, tiered framework within which candidates can be evaluated and integrated.

Conclusions and future directions

The accumulated mechanistic, preclinical, and human evidence now justifies viewing the thymus as a central node in adult immune aging and as a plausible therapeutic target [1–3, 5–9, 11–13, 20–25]. Thymic involution contributes to reduced naïve T-cell output, contracted

TCR repertoire diversity, impaired central tolerance, and altered tissue-specific immune surveillance, which in turn intersect with the major hallmarks of aging and with clinical domains including cancer, infection, autoimmunity, cardiovascular disease, neurodegeneration, and frailty [2, 3, 5–9, 11–13, 20, 23–25, 29]. At the same time, the aged thymus retains epithelial stem and progenitor cells, endogenous regenerative signals, and plasticity that can be harnessed experimentally, albeit in the face of age-associated epithelial defects and systemic inhibitory cues [14–19, 22, 23, 30, 31, 35–41].

Future research should prioritize three broad directions. First, there is a clear need for well-powered, domain-focused clinical trials of thymus-directed interventions in carefully defined populations, such as older adults at high risk of severe infection, patients with poor immune reconstitution after chemotherapy, hematopoietic stem-cell transplantation or HIV, and selected cancer cohorts in which thymic status may plausibly influence immunotherapy outcomes [5, 9, 11–13, 20–22, 24–29, 45, 46]. Such studies should move beyond imaging alone and employ harmonized biomarker panels—including quantitative thymic imaging, TCR excision circles and recent thymic emigrant measurements, naïve and memory T-cell subsets, TCR repertoire diversity, and vaccine or infection endpoints—so that structural, immunological, and clinical effects can be related quantitatively [4–6, 9, 11, 13, 21, 22, 24, 25, 28, 33, 36–39, 45, 46].

Second, mechanistic human studies are needed to clarify how age-associated epithelial states, inflammatory niches, and systemic factors such as sex steroids, FGF21, and somatotrophic signaling constrain or support regeneration in older thymi, building on recent work in mouse and organoid systems [9, 14–19, 23, 36, 38, 39, 42].

Third, preclinical development should increasingly focus on strategies that integrate insights from epithelial stem-cell biology, stromal–immune crosstalk, and comparative regeneration. The existence of human thymic epithelial stem cells and successful reconstitution of functional thymus from postnatal stromal progenitors support the feasibility of cell-based and tissue-engineering approaches as complements or alternatives to purely systemic therapies [14–17, 22, 23, 30]. Likewise, gene- and protein-based strategies that target thymic epithelial cells and their signaling environment—FOXN1, IL-22, IL-7, KGF/BMP4, FGF21, AIRE, and telomerase—should be refined with an emphasis on epithelial specificity, transient modulation, and integration with endogenous regenerative programs rather than wholesale reprogramming of the organ [14–19, 31, 33–42]. Across all modalities, safety will require particular attention in older and comorbid populations, with systematic monitoring for autoimmunity, clonal expansions, and off-target effects,

especially in the context of gene therapy and potent growth factors [6, 9, 10, 13–15, 28, 33–41, 43, 54].

To move from conceptual rationale to clinical reality, at least three priority trial archetypes can be envisioned. First, in older adults (≥ 65 years) at high risk of severe infection, a hormonal or cytokine-based thymic support regimen could be evaluated with co-primary endpoints of laboratory-confirmed infection incidence and vaccine seroconversion rates, using TREC levels and naïve T-cell counts as mechanistic biomarkers.

Second, in patients with immune reconstitution failure after hematopoietic stem-cell transplantation or intensive chemotherapy, adjunctive IL-22, KGF/BMP4, or engineered thymic epithelial progenitor cell products could be tested against primary endpoints of TREC recovery kinetics, TCR repertoire diversity, chronic graft-versus-host disease incidence, and infection-free survival.

Third, in HIV immunological non-responders with persistently low CD4⁺ counts despite virological suppression, thymus-directed interventions could target recent thymic emigrant counts, CD4⁺ reconstitution trajectory, and rates of non-AIDS-defining events as primary and secondary endpoints. Each of these archetypes would require harmonized biomarker panels integrating quantitative thymic imaging, functional immune readouts, and hard clinical endpoints, thereby generating the domain-specific evidence base that is currently lacking [5, 9, 11–13, 20–22, 24–29, 45, 46].

Ultimately, thymus-directed interventions should be situated within a broader framework of healthy aging and systems-level immune maintenance rather than presented as stand-alone solutions. Reviews of age-related thymic involution increasingly emphasize that thymic decline is intertwined with chronic inflammation, metabolic dysregulation, and tissue-specific aging processes, and that restoring thymic output alone is unlikely to reverse all downstream pathology [3, 5, 6, 8–10, 23]. Conceptually, thymus-targeted therapies may be most effective when combined with interventions that address complementary aspects of aging biology—such as senescent-cell burden, clonal hematopoiesis, mitochondrial dysfunction, and neuroinflammation—within rational, indication-specific treatment programs [3, 8–13, 20, 23, 29, 53, 54]. By pursuing coordinated basic, translational, and clinical research along these lines, the field can determine whether and how thymus regeneration can move from a compelling mechanistic hypothesis to a practical component of strategies to extend immune healthspan and reduce the burden of age-associated disease [2, 3, 5–20, 22–25, 28, 29, 31–42].

Abbreviations

AIRE	Autoimmune regulator
ART	Antiretroviral therapy
BMP4	Bone morphogenetic protein 4

cGVHD	Chronic graft-versus-host disease
cTEC	Cortical thymic epithelial cell
FGF21	Fibroblast growth factor 21
FOXN1	Forkhead box N1
HSCT	Hematopoietic stem-cell transplantation
IGF-1	Insulin-like growth factor 1
IL	Interleukin
KGF	Keratinocyte growth factor
mTEC	Medullary thymic epithelial cell
SASP	Senescence-associated secretory phenotype
TCR	T-cell receptor
TEC	Thymic epithelial cell
TREC	T-cell receptor excision circle
Treg	Regulatory T cell

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