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Systems Regeneration in Hashimoto Thyroiditis: Integrating Thyroid Precursor Cells, Mitochondrial Therapeutics, and Organ-Specific Peptide Signaling

Mike KS Chan[1,2,3], Michelle BF Wong[1,2], Dmytro Klokol[1,2], Krista Casazza[4] and Jonathan RT Lakey[2,4*]

[1]European Wellness Academy, Klosterstrasse 205ID, 67480, Edenkoben, Germany
[2]European Wellness BioMedical Group, Klosterstrasse 205ID, 67480, Edenkoben, Germany
[3]Lincoln University College, Selangor, Malaysia
[4]University of California, Irvine, Department of Surgery and Biomedical Engineering, Irvine CA, USA

***Corresponding author:** Jonathan RT Lakey, PhD, MSM, Professor Emeritus, Departments of Surgery and Biomedical Engineering, University of California Irvine, USA

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Abstract

Hashimoto thyroiditis (HT) is a chronic autoimmune disorder in which progressive immune-mediated follicular injury can culminate in irreversible loss of thyroid function. Levothyroxine effectively corrects hormone deficiency but does not restore damaged follicular architecture or directly re-establish thyroid-directed immune tolerance. Emerging advances in thyroid developmental biology, organoid systems, mitochondrial medicine, and peptide signaling provide a rationale for investigating whether tissue preservation and regeneration could complement endocrine replacement. This review develops a systems-regeneration framework in which HT is considered an immune–endocrine tissue disorder involving three interdependent therapeutic domains: loss of functional thyroid follicular cells, metabolic and mitochondrial stress, and dysregulated tissue–immune signaling. Thyroid-specified precursor/progenitor cells (PSCs) provide a candidate cellular substrate for follicular reconstruction; mitochondrial-directed therapeutics and Mito Organelle (MO) biologics provide a testable strategy for supporting metabolic competence; and organ-specific Nano Organo Peptides (NOPs) and targeted peptides provide candidate tissue-contextual and immunoregulatory signals. Within this framework, the European Wellness platform is evaluated as a candidate implementation integrating PSC, MO, and NOP modalities rather than as an established treatment for HT. Critical translational requirements include molecular product characterization, demonstration of thyroid-specific identity and potency, immune–thyroid co-culture and organoid studies,

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factorial testing of individual and combined components, and validation in autoimmune thyroiditis models before controlled clinical investigation. The appropriate benchmark for regenerative efficacy is not normalization of thyroid biomarkers alone, but durable preservation or restoration of functional thyroid tissue without exacerbation of thyroid-directed autoimmunity.

Keywords

Hashimoto thyroiditis; Autoimmune thyroiditis; Thyroid regeneration; Thyroid organoids; Precursor/progenitor cells; Mitochondrial dysfunction; Peptide signaling; Nano Organo Peptides; Mito Organelles; Regenerative endocrinology.

Introduction

Hashimoto Thyroiditis as a Failure of Immune–Endocrine Tissue Homeostasis

Hashimoto thyroiditis (HT) is the most prevalent autoimmune thyroid disorder and a major cause of acquired hypothyroidism [1,2]. Its defining pathology extends beyond reduced circulating thyroid hormone: progressive lymphocytic infiltration, autoantibody-associated thyroid autoimmunity, inflammatory injury to thyroid follicular cells (TFCs), oxidative stress, and loss of functional follicular architecture progressively reduce the gland's capacity to synthesize and secrete thyroid hormone1–3. Levothyroxine effectively restores circulating hormone concentrations in most patients who develop hypothyroidism, but it functions as endocrine replacement rather than thyroid regeneration [2,3]. It neither reconstructs damaged follicles nor directly restores immune tolerance to thyroid antigens. This therapeutic distinction provides the rationale for investigating whether regenerative approaches could complement, rather than replace, conventional hormone replacement.

The thyroid is a compelling regenerative target because endocrine function depends on highly organized follicular architecture and a defined developmental program governed principally by NKX2-1 and PAX8, followed by acquisition of mature functions including iodide transport, thyroglobulin synthesis and iodination, and regulated hormone secretion [1]. Experimental specification of thyroid progenitors demonstrates that functional thyroid identity can, in principle, be reconstructed [4,5]. Adult human TFC-derived organoids retain canonical thyroid markers including PAX8 and NKX2-1, reproduce polarized follicular architecture, and possess machinery required for thyroid-hormone production [6,7]. Notably, human ESC-derived thyroid organoids generated through developmental programming of NKX2-1 and PAX8 have formed functional follicles and restored circulating thyroid hormone in athyreotic mice, providing proof of principle for thyroid tissue reconstruction [4]. Recent work has also generated transplantable NKX2-1^+/PAX8^+ thyroid follicular epithelial cells from human iPSCs, although those cells did not rescue hypothyroidism after transplantation, underscoring the distinction between acquisition of thyroid lineage markers and demonstration of therapeutic function [5], a distinction central to HT. Replacing TFCs without correcting the environment responsible for their destruction would leave newly generated tissue exposed to the same autoimmune pressure. Conversely, suppressing inflammation without restoring sufficiently damaged follicular tissue cannot necessarily recover lost endocrine capacity [8]. For purposes of regenerative therapeutics, HT represents an immune–endocrine systems disorder in which cellular identity, immune tolerance, metabolic competence, and tissue-specific signaling intersect. These findings establish both the feasibility and the central limitation of thyroid cell regeneration, i.e., lineage specification is necessary but does not establish therapeutic function.

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Why Thyroid Regeneration Fails

Regenerative failure in HT reflects the convergence of persistent thyroid-directed immunity, oxidative/metabolic stress, and loss of functional follicular identity [1-3]. T and B lymphocytes, antigen-presenting cells, autoantibodies, inflammatory cytokines, and thyrocyte-intrinsic responses establish an environment in which newly generated as well as residual TFCs remain vulnerable to immune-mediated injury [9]. Consequently, regeneration cannot be defined by thyroid-cell proliferation alone; durable disease modification requires preservation or reconstruction of functional follicles within an immune environment permissive for their survival [10]. Oxidative and mitochondrial stress add an additional constraint such that physiological thyroid-hormone synthesis requires tightly controlled redox chemistry, while autoimmune thyroiditis is associated with imbalance between oxidant generation and antioxidant defenses [3]. Mitochondrial dysfunction may therefore couple inflammatory stress to impaired TFC survival and metabolic competence, providing a mechanistically plausible regenerative target without establishing that mitochondrial preparations themselves treat HT [11]. Additionally, regeneration requires restoration of authentic thyroid identity. The ability to produce NKX2-1^+/PAX8^+ progenitors or even TG-expressing cells is not equivalent to restoration of a functional thyroid gland [12]. Therapeutically meaningful regeneration requires organized follicles capable of iodide uptake, thyroglobulin processing, hormone synthesis and release, TSH responsiveness, and sustained function in an autoimmune host [13]. The organoid literature provides the experimental tools necessary to evaluate these endpoints directly [14]. The central regenerative problem in HT is therefore not simply insufficient thyroid hormone production, but failure to preserve or reconstruct functional follicular tissue within an immune and metabolic environment capable of sustaining it [13].

A Three-Domain Systems-Regeneration Framework for Hashimoto Thyroiditis

Thyroid-directed precursor/progenitor cells (PSCs) represent the structural domain for preservation or reconstruction of functional follicular epithelium [15]. The appropriate developmental benchmark is not generic stemness but demonstrable thyroid specification, including NKX2-1/PAX8 identity followed by acquisition of mature TG, TPO, TSHR, NIS/SLC5A5 and functional follicular characteristics [16]. Human organoid and pluripotent-cell studies provide strong proof of principle that such thyroid-lineage reconstruction is biologically achievable. They do not, however, demonstrate that an incompletely characterized organ-derived PSC preparation possesses equivalent thyroid-regenerative activity [17].

Mitochondrial-directed therapeutics, including mitochondrial-derived peptides and MO biologics, constitute the metabolic domain. Their proposed role is to support the metabolic competence required for TFC survival and function through mechanisms that may include modulation of bioenergetics, redox homeostasis, mitochondrial quality control, and organelle-associated inflammatory signaling [18].

NOPs and defined targeted peptides constitute the tissue-signaling domain. Thyroid-derived NOPs provide a testable source of tissue-contextual signals affecting TFC survival, differentiation, and follicular organization, whereas thymic/immune- and placenta-derived preparations provide separate hypotheses involving immunoregulation, vascular support, or stress adaptation [19]. Organ of origin alone, however, does not establish target-organ specificity. This yields the system-driven hypotheses that 1) thyroid PSCs provide the cellular substrate for follicular reconstruction; 2) MO and other mitochondrial-directed

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biologics support metabolic competence; and 3) thyroid- and immune-directed NOPs provide tissue-contextual and immunoregulatory signaling [20]. The scientific rationale for this model is that each therapeutic domain addresses a distinct but interdependent constraint on thyroid regeneration. Their integration may therefore provide greater biological benefit than any individual component by simultaneously supporting follicular reconstruction, metabolic competence, and tissue-specific immune regulation [21].

Thyroid PSCs and Follicular Reconstruction

Adult thyroid-derived organoids demonstrate self-renewal and differentiation into thyroid-like tissue, while human pluripotent stem cells can be developmentally specified toward thyroid progenitors through NKX2-1/PAX8-centered programs [22]. For an organ-matched thyroid PSC preparation, developmental or anatomical source should therefore be treated as a starting hypothesis rather than evidence of identity [20]. A candidate thyroid PSC product would require molecular confirmation of thyroid-lineage identity, ideally at single-cell resolution, together with functional demonstration of follicle formation, polarization, iodide uptake and organification, TSH responsiveness, and T4/T3 production [5]. Genomic stability, proliferative control, and exclusion of inappropriate lineage populations are additional prerequisites. Immune compatibility with the disease environment of HT creates an additional requirement [23]. A PSC that forms follicles in an immunodeficient mouse has not demonstrated resistance to autoimmune thyroid destruction [24]. Appropriate translational models must therefore incorporate thyroid-directed immunity and assess whether regenerated cells become targets of recurrent immune injury.

MO Biologics and Mitochondrial Rescue

Oxidative imbalance is consistently associated with autoimmune thyroiditis, while mitochondrial biology influences redox control, cell survival and thyroid metabolic function [25,26]. Thus, an organelle-derived intervention may provide a testable means of improving TFC metabolic resilience, particularly under inflammatory stress. Before therapeutic claims are appropriate, the MO preparation itself must be compositionally defined. Whether it contains intact respiratory-competent mitochondria, membrane fragments, mitochondrial proteins or peptides, nucleic acids, metabolites, or a mixture of these constituents fundamentally determines its plausible mechanism, pharmacology, and appropriate potency assays. Disease-relevant validation is used to determine whether MO treatment preserves mitochondrial function and thyroid-specific competence in primary human TFCs or thyroid organoids exposed to inflammatory stress. Mitochondrial endpoints can be coupled to follicular polarity, thyroid-lineage markers, iodide handling, hormone production, and survival. It is critical to evaluate immunomodulatory activity independently rather than inferred from antioxidant effects.

NOPs and Targeted Peptide Signaling at the Thyroid–Immune Interface

NOPs represent the most compositionally and mechanistically uncertain component of the framework and therefore require particularly rigorous analytical characterization. Tissue-derived peptide fractions cannot be presumed to retain developmental “information” simply because they originate from thyroid, thymus, placenta or another organ [27]. Organ specificity is an experimentally testable pharmacological property. Thyroid-directed preparations for follicular differentiation and endocrine function; immune/thymic preparations for thyroid-directed immune regulation; and placenta-derived preparations

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for immunoregulatory, vascular, or cytoprotective activity require evaluation according to function rather than source alone [5,15]. A biologic that broadly stimulates thyroid-cell growth without reducing autoimmune recognition could expand antigenic substrate; conversely, an immunoregulatory preparation that reduces inflammation may preserve remaining follicles without regenerating those already lost. The optimal peptide architecture may therefore depend on disease stage and residual functional thyroid mass.

European Wellness as a Testable Platform

The European Wellness (EW) platform provides a candidate implementation of this three-domain architecture by integrating organ-matched PSCs, MO biologics, and organ-derived NOP preparations [28-31]. Its scientific rationale is not that any component has established regenerative efficacy in HT, but that each is intended to address a distinct biological constraint. Notably, PSCs provide a candidate cellular substrate for follicular reconstruction, MO biologics target metabolic competence, and NOPs provide candidate tissue-contextual or immunoregulatory signals. Existing EW studies provide an analytical and translational foundation for investigating these modalities, but direct demonstration of thyroid-specific activity, organ selectivity, and therapeutic interaction remains necessary.

Development from product characterization to mechanistic testing in human thyroid organoids and immune–thyroid co-culture systems are followed by autoimmune-thyroiditis models. Factorial designs subsequently evaluate PSC, MO, and NOP components individually, pairwise, and in combination to distinguish independent activity from additive or synergistic effects. Mechanism-linked endpoints should encompass thyroid identity and follicle formation, iodide handling and hormone synthesis, mitochondrial function, inflammatory injury, and relevant immune phenotypes. Only combinations demonstrating reproducible, mechanistically interpretable benefit should advance toward clinical investigation. Evidence of regeneration would instead require prespecified demonstration of improved endogenous thyroid secretory reserve and/or reduced replacement-hormone requirement, supported by structural or functional evidence of preserved or restored thyroid tissue and sustained control of thyroid-directed autoimmunity.

Conclusions

HT illustrates a fundamental challenge for regenerative endocrinology: restoration of endocrine function requires more than replacement of deficient hormone or generation of new thyroid-lineage cells. Durable thyroid regeneration would require preservation or reconstruction of functional follicular architecture within an environment in which immune-mediated injury and metabolic stress are sufficiently controlled to permit sustained tissue function. A systems-regeneration framework integrating thyroid-specified PSCs, mitochondrial-directed therapeutics, and tissue- or immune-directed peptide signaling provides a testable approach to these complementary constraints. PSCs offer a candidate substrate for follicular reconstruction, MO biologics target metabolic competence, and NOPs provide candidate tissue-contextual or immunoregulatory signals. These domains should not be presumed to be individually effective or synergistic; identity, mechanism, potency, tissue specificity, and interaction must each be demonstrated experimentally. The EW platform provides a candidate implementation of this architecture, but its advancement in HT now requires molecular product characterization, mechanism-linked potency assays, human thyroid organoid and immune–thyroid models, autoimmune disease models, and

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ultimately controlled clinical investigation. The relevant translational benchmark is not generalized immunomodulation, changes in thyroid autoantibodies, or normalization of TSH during hormone replacement, but durable preservation or restoration of endogenous thyroid function without exacerbation of thyroid-directed autoimmunity.

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