THYMIC REJUVENATION PROTOCOL

Scientific & Clinical Reference

A pharmacologically detailed framework for thymic immunosenescence reversal targeting cTEC/mTEC regeneration, GH/IGF-1-axis stimulation, mTOR-mediated senescent cell clearance, and iterative 4-week cycling for longevity co-objectives.

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OVERVIEW

Executive Summary

Thymic involution begins at puberty and reduces naive T-cell output by >90% between ages 20 and 70. This protocol addresses it through three axes: (1) GH/IGF-1 stimulation of cTEC/mTEC proliferation via tesamorelin; (2) direct T-cell maturation support via thymosin a1; (3) mTOR inhibition and senescent-cell clearance via rapamycin in an off-tesamorelin clearance week. These axes are supported by a daily base stack of six compounds selected on mechanistic relevance and safety grounds.

#	Component	Dosing	Phase	Primary Mechanism
1	DHEA	25-50mg po AM	Daily	AR on TECs; androgen precursor
2	Imeglimin	500-1000mg dinner	Daily	Mitochondrial ROS; GSIS
3	Zinc + Copper	Zn 20mg+Cu 2mg AM	Daily	Thymulin cofactor; antioxidant
4	D3 + K2	3-5kIU D3 + 150mcg K2	Daily	VDR on TECs; calcium homeostasis
5	Omega-3	2-3g with meals	Daily	NF-kB/NLRP3 suppression
6	Melatonin	0.3mg pre-sleep	Daily	MT1/MT2 on TECs; somatostatin suppression
7	Tesamorelin	2mg SC bedtime	Wks 1-3	GHRH-R agonist; pulsatile GH; IGF-1
8	Thymosin a1	1.6mg SC 2x/wk	All weeks	T-cell maturation; TEC cytokines; TLR9
9	Rapamycin	5mg po Mon fasted	Wk 4 only	FKBP12/mTORC1; autophagy; SASP suppression

Table 1: Protocol overview. Wks 1-3=thymopoiesis; Wk 4=clearance.

SECTION 1

Thymic Biology & Immunosenescence

1.1 Thymic Architecture

The thymus is a bilobed primary lymphoid organ organised into cortex and medulla. **Cortical TECs (cTECs)** express b5t (PSMB11) and cathepsins L/B generating a specialised MHC II ligandome for positive selection of $CD4^+$ T cells. **Medullary TECs (mTECs)** uniquely express AIRE, driving ectopic expression of tissue-restricted antigens for central tolerance via negative selection.

FoxN1 - Master TEC Regulator. Non-redundant transcription factor for TEC specification and maintenance. Homozygous loss = nude phenotype (athymic). FoxN1 declines with age via reduced androgen signalling and epigenetic silencing. GH receptor activation on cTECs stimulates FoxN1 via JAK2/STAT5 - primary tesamorelin rationale. (Sun et al., Nat Immunol 2018)

1.2 Thymocyte Development Pathway (~3-week transit ETP to naive T cell)

Stage	Surface Phenotype	Location	Key Events
ETP/DN1	$CD44^{hi}CD25^{-}CD117^{hi}$	CMJ	Notch1 commitment
DN2-4	CD44/CD25 progression	Subcapsule-Cortex	TCR rearrangement; beta-selection
DP	$CD4^+CD8^+$	Cortex	Positive selection by cTEC MHC-peptide
SP CD4/CD8	Single-positive TCR^{hi}	Medulla	Negative selection/Treg diversion by mTEC-AIRE
Naive T	$CD62L^{hi}CCR7^+CD45RA^+$	Exits	Recirculates as naive T cell

Table 2: Thymocyte developmental stages. DN=double-negative; DP=double-positive; CMJ=corticomedullary junction.

1.3 Mechanisms of Thymic Involution

Mechanism	Molecular Basis	Protocol Target
Sex steroid FoxN1 suppression	AR/ER on TECs suppress FoxN1; peri-pubertal involution acceleration	DHEA: partial AR antagonism; precursor substrate
GH/IGF-1 axis decline	Somatotrophic axis falls ~14%/decade; TECs express GHR and IGF-1R	Tesamorelin: GHRH-R agonist restoring pulsatile GH
TEC senescence & SASP	Telomere attrition, ROS, mTORC1 hyperactivation drive senescence; IL-6/IL-1b/TNF-a toxic to thymocytes	Rapamycin: mTORC1 inhibition; omega-3/melatonin: NF-kB/NLRP3
Adipogenic replacement	PPAR-g-driven adipocytes replace TEC mass; perivascular infiltration disrupts TEC-thymocyte contacts	Tesamorelin: GH lipolytic action on thymic adipocytes (TRIIM MRI)

ETP progenitor attrition	Reduced CLP output; diminished thymic homing (CCR7, CXCR4)	Thymosin a1: T-cell maturation support; indirect ETP support

Table 3: Involution mechanisms and protocol targets. SASP=senescence-associated secretory phenotype.

1.4 sjTREC Biomarkers

sjTRECs are episomal DNA by-products of TCR-alpha rearrangement in DP thymocytes. Not replicated during peripheral division, so sjTREC abundance in blood tracks recent thymic emigrants (RTEs). Quantified by qPCR on PBMC DNA - the most cost-accessible direct thymic output readout. TRIIM used sjTREC as primary immunological endpoint (Fahy et al., Aging Cell 2019).

SECTION 2

GH/IGF-1 Axis - Signal Transduction & TRIIM Evidence

2.1 GHRH Receptor Signalling Cascade

Tesamorelin is a synthetic GHRH analogue (44 AA + trans-3-hexenoic acid N-terminal modification) resistant to DPP-4 cleavage, extending t1/2 from ~7 min (native GHRH) to ~26 min. Binds GHRH-R (class B1 Gs-coupled GPCR) on pituitary somatotrophs.

Step	Molecular Event	Key Mediators
1	GHRH-R Gs-coupled activation	Tesamorelin binds; Gs-alpha activated
2	Adenylyl cyclase	cAMP rises 5-10x
3-4	PKA + CREB phosphorylation	PKA catalytic release; pCREB Ser133; CBP/p300 recruitment
5-6	GH gene expression and secretion	Pit-1 co-occupancy; pulsatile GH release; bedtime aligns with somatostatin nadir
7	Hepatic IGF-1 production	GHR/JAK2/STAT5b cascade; IGFBP-3 bound IGF-1 (t1/2 ~15h)
8	TEC IGF-1R activation	PI3K/AKT/mTORC1 (proliferation) + MAPK/ERK (survival/cycling) arms on cTEC/mTEC

Table 4: GHRH-R signalling cascade.

2.2 IGF-1/mTOR Signalling Tension

IGF-1R on TECs activates PI3K/AKT/mTORC1, driving TEC proliferation and FoxN1 expression. This is the same arm inhibited by rapamycin - the protocol's central pharmacological conflict, resolved by pausing tesamorelin during clearance weeks and providing >7 days of IGF-1 pharmacodynamic washout before and after rapamycin.

2.3 TRIIM Trial Summary

Parameter	Details
Design	Phase II open-label pilot; n=9 males aged 51-65; 12 months treatment
Interventions	rhGH 0.015mg/kg/day SC + DHEA 50mg/day + metformin 500mg BID
Thymic MRI	Significant fat fraction reduction (p=0.02); thymic parenchyma visible in 7/9
sjTREC	Mean increase ~100 to ~250 copies/10^6 PBMCs at 12 months
GrimAge clock	Mean biological age -2.5 years (p<0.05); persisted at 6-month follow-up
Immune	Increased naive $CD4^+$/$CD8^+$; decreased Treg frequency
Adaptation here	rhGH replaced by tesamorelin (preserves pulsatility); metformin replaced by imeglimin (no AMPK/mTOR interference)

Table 5: TRIIM trial. rhGH=recombinant human growth hormone.

SECTION 3

mTOR Pathway, Rapamycin Mechanism & Thymic Senescence

3.1 mTORC1 vs mTORC2

Feature	mTORC1	mTORC2
Unique subunit	Raptor	Rictor
Rapamycin	Acutely sensitive (FKBP12-rapamycin)	Relatively insensitive
Substrates	S6K1 (Thr389), 4EBP1, ULK1	AKT (Ser473), SGK1, PKC-a
Functions	Protein synthesis, autophagy inhibition, cell growth	Cytoskeleton, glucose metabolism, survival
In TECs	Drives proliferation; hyperactivation drives senescence	AKT survival signalling
Protocol	Primary rapamycin target; downstream of tesamorelin (phase separation required)	Not targeted at protocol doses

Table 6: mTORC1 vs mTORC2.

3.2 Rapamycin Mechanism (FKBP12)

Rapamycin binds FKBP12 (Kd ~0.2 nM). The binary complex binds the FRB domain of mTOR, blocking Raptor-mediated substrate recruitment to mTORC1. S6K1 and 4EBP1 phosphorylation blocked within 30-60 min. ULK1 de-repression restores autophagy, clearing damaged organelles and suppressing cGAS-STING/NF-kB SASP amplification.

PEARL Trial (2025, n=256, 24 weeks, 5mg/week): No statistically significant infection increase vs placebo in healthy adults. NIA ITP: 9-14% lifespan extension in genetically heterogeneous mice. Protocol uses 5mg every 4th week (13 doses/year) - conservative longevity cadence prioritising thymic biology.

3.3 Thymic Senescence and SASP

SASP Component	Source	Effect on Thymic Function
IL-6	Senescent mTECs	Drives adipogenesis (PPAR-g); inhibits FoxN1; disrupts cTEC/DP interaction
IL-1b	NLRP3 inflammasome	NF-kB amplification; thymocyte apoptosis induction
TNF-a	Senescent cells	Involution acceleration; RANK-L pathway disruption
MCP-1	Senescent TECs	Macrophage recruitment; pro-inflammatory amplification
MMPs	Senescent stroma	ECM remodelling; disrupts TEC scaffold

Table 7: SASP in thymic senescence. NLRP3=NOD-like receptor pyrin domain-containing 3.

SECTION 4

Component Pharmacology - Primary Agents

4.1 Tesamorelin

Class: Synthetic GHRH analogue. **FDA:** Approved (Egrifta SV) for HIV lipodystrophy.

PK Parameter	Value
MW	5135 Da (44 AA + trans-3-hexenoic acid)
Route	SC injection
Bioavailability	~3-4% SC
Tmax	~0.15h
Cmax (2mg SC)	~6.7 ng/mL
t1/2	~26 min
Vd	~9.4 L/kg
Metabolism	Endopeptidase; DPP-4 resistant
IGF-1 plateau	7-10 days; washout 2-4 wks post-cessation
Protocol dose	2mg SC bedtime, thymopoiesis weeks

Table 8: Tesamorelin PK.

Bedtime dosing: Aligns with somatostatin nadir during early slow-wave sleep, amplifying the natural GH pulse. Melatonin (0.3mg) provides mild hypothalamic somatostatin suppression, complementarily amplifying the nocturnal GH pulse.

Phase III (CALM, n=403): Trunk fat -15.2% vs +5.0% ($p<0.0001$); IGF-1 +126 ng/mL; visceral adipose -18.3% by CT.

4.2 Thymosin a1 (Ta1)

Class: Synthetic thymic peptide. **Status:** Approved >35 countries (Zadaxin).

PK Parameter	Value
MW	3108 Da; 28 AA
Route	SC injection
Bioavailability	~100% SC
Tmax	~2h
Cmax (1.6mg)	~25.6 ng/mL
t1/2	~2h
Vd	~19L
Metabolism	Peptide hydrolysis; no CYP450
Receptor targets	TLR9/MyD88; thymosin-specific receptors on immature T cells
Protocol dose	1.6mg SC Tuesday + Friday, ALL weeks (continuous)

Table 9: Thymosin a1 PK.

Mechanisms: (1) Promotes $CD3^-$ to $CD3^+$ differentiation; upregulates CD3/CD4/CD8/IL-2R. (2) Stimulates mTEC secretion of thymopoietin, thymulin, thymosin b4. (3) TLR9/pDC pathway supports $AIRE^+$ mTEC maintenance. (4) Treg:Teff shift toward effectors without autoimmunity. **Continuous use:** Acts on T-cell maturation (not TEC proliferation), no mTOR conflict, provides TEC support during clearance weeks when tesamorelin is paused.

4.3 Rapamycin (Sirolimus)

Class: Macrolide; mTORC1 inhibitor. **FDA:** Approved (Rapamune) for renal transplant and LAM.

PK Parameter	Value
MW	914 Da
Route	Oral
Bioavailability	~14-15% (CYP3A4/P-gp first-pass)
Food effect	High-fat +35% AUC; take fasted
Tmax (fasted)	1-3h
Cmax (5mg)	~14.4 ng/mL
t1/2	~62h (range 46-78h)
Vd	~12 L/kg; extensive tissue distribution
Metabolism	Primarily CYP3A4; P-gp substrate
Protein binding	~92%
Key CYP interaction	Azoles/grapefruit increase AUC 2-10x; rifampicin reduces
Protocol dose	5mg po Monday fasted, clearance week only (13 doses/year)

Table 10: Rapamycin PK. CYP3A4=cytochrome P450 3A4.

4.4 Imeglimin

Class: Tetrahydrotriazine; mitochondrial complex I modulator. **Status:** Approved Japan (Twymeeg, 2021).

PK Parameter	Value
MW	254 Da
Route	Oral
Bioavailability	~51%
Tmax	1-3h
Cmax (1000mg)	~13 mcg/mL
t1/2	~11h
Vd	~148L
Metabolism	Minimal hepatic; primarily unchanged renal excretion
Renal dose	Reduce if eGFR 30-45; contraindicated <30
vs Metformin	Reduces mito ROS + restores KATP + enhances GSIS; no AMPK/mTOR interference; no lactic acidosis risk
Protocol dose	500-1000mg po with dinner daily

Table 11: Imeglimin PK. eGFR=estimated glomerular filtration rate; GSIS=glucose-stimulated insulin secretion.

Rationale over metformin: Metformin activates AMPK->TSC2->mTOR inhibition, partially attenuating the IGF-1/mTOR TEC proliferative signal. Imeglimin acts via mitochondrial ROS and KATP, not intersecting the GH/IGF-1/mTOR axis. During clearance weeks, imeglimin buffers rapamycin-induced insulin resistance.

SECTION 5

Component Pharmacology - Daily Base Stack

Component	Dose	Primary Targets	Thymic Relevance	Key Evidence
DHEA	25-50mg AM	AR, ER (precursor); sigma-1R	Partial AR antagonism on TECs reduces FoxN1 suppression; DHEA-S falls ~2%/yr paralleling involution	Fahy 2019; Napolitano 2008
Imeglimin	500-1000mg dinner	Mito complex I; KATP; GSIS	TEC mitochondrial protection; buffers rapamycin insulin resistance	Hallakou-Bozec 2021; Vial 2011
Zn 20mg+Cu 2mg	Morning	Thymulin (Zn2+ cofactor); Cu/Zn-SOD	Thymulin/FTS requires Zn2+; deficiency causes thymic atrophy; Cu prevents depletion	Haase & Rink 2009
D3 3-5kIU+K2 150mcg	With fat	VDR nuclear receptor; MGP (K2)	VDR on cTEC/mTEC; 1,25D3 promotes AIRE; target 40-60 ng/mL 25-OH-D	Adorini & Penna 2008
Omega-3 2-3g	With meals	GPR120; NF-kB; NLRP3; SPMs	NF-kB/NLRP3 suppression reduces SASP; resolvins (RvD1, RvE1) resolve inflammation	Calder 2017; Serhan 2018
Melatonin 0.3mg	Pre-sleep	MT1/MT2 on TECs; mito ROS; somatostatin	Physiological dose preserves receptor sensitivity; amplifies tesamorelin GH pulse	Guerrero & Reiter 2002

Table 12: Daily base stack. VDR=vitamin D receptor; SASP=senescence-associated secretory phenotype; SPMs=specialised pro-resolving mediators.

SECTION 6

Protocol Architecture - 4-Week Cycle Design

6.1 Rationale for 3:1 Cycle Ratio

Constraint	Biological Basis	Protocol Implication
Thymocyte maturation	ETP-to-naive transit ~3 weeks; shorter windows terminate before full cohort completes	Minimum 3-week thymopoiesis block
Annual tesamorelin	TRIIM used ~240 days/yr; 3:1 cycle yields 274 days/yr (3/4 x 365)	No loss of annual TEC stimulation
Rapamycin cadence	Once-weekly validated longevity dose; monthly (13x/yr) balances senolysis vs glucose effects	13 doses/year: meaningful mTOR inhibition without continuous immunosuppression
IGF-1/mTOR separation	mTORC1 inhibition persists ~48-72h; full week off tesamorelin gives >7-day IGF-1 washout	Complete pharmacological separation of the signalling conflict

Table 13: Biological constraints for 3:1 cycle.

6.2 Weekly Schedule Template

Day	Thymopoiesis Weeks (1-3)	Clearance Week (4)
Monday	Tesamorelin 2mg SC bedtime; Base stack	**Rapamycin 5mg po fasted AM**; Base stack (NO tesamorelin)
Tuesday	Tesamorelin 2mg SC; Thymosin a1 1.6mg SC; Base stack	Thymosin a1 1.6mg SC; Base stack (NO tesamorelin)
Wed-Thu	Tesamorelin 2mg SC bedtime; Base stack	Base stack (NO tesamorelin)
Friday	Tesamorelin 2mg SC; Thymosin a1 1.6mg SC; Base stack	Thymosin a1 1.6mg SC; Base stack (NO tesamorelin)
Sat-Sun	Tesamorelin 2mg SC bedtime; Base stack	Base stack (NO tesamorelin)

Table 14: Weekly schedule. Base stack = DHEA, Imeglimin, Zinc+Cu, D3+K2, Omega-3, Melatonin.

6.3 Annual Exposure

Component	Doses/Year	Active Days	Notes
Daily base stack	365	365	Continuous
Tesamorelin 2mg	~274	~274	3/4 x 365; matches TRIIM annual exposure
Thymosin a1 1.6mg	~104	N/A	2x/week x 52
Rapamycin 5mg	~13	N/A	1x per clearance week

Table 15: Annual exposure summary.

SECTION 7

Pharmacological Interactions

Pair	Type	Mechanism	Management
Tesamorelin + Rapamycin	Antagonistic (managed)	IGF-1/AKT/mTORC1 vs mTORC1 inhibition	Resolved by phase separation; 7+ day washout
Rapamycin + Imeglimin	Complementary	Rapa impairs IRS-1 signalling; imeglimin enhances GSIS/mito ROS	No adjustment; imeglimin continues daily
Tesamorelin + Melatonin	Synergistic	Melatonin suppresses somatostatin, amplifying GH pulse	Beneficial; no monitoring required
Tesamorelin + DHEA	Additive	DHEA reduces AR-mediated FoxN1 suppression; tesamorelin restores IGF-1/GHR FoxN1	Both in TRIIM; no adverse interactions
Rapamycin + Thymosin a1	Compatible	Ta1 via TLR9/MyD88; not mTORC1 - no conflict	None; Ta1 continues through clearance
Rapamycin + CYP3A4 inhibitors	Clinically significant	Azoles/grapefruit can increase rapa AUC 2-10x	Avoid azoles and grapefruit in clearance week
Zinc + Copper ratio	Antagonistic at high Zn	Excess Zn inhibits Cu absorption via metallothionein	Fixed ratio: Zn 20mg + Cu 2mg daily

Table 16: Pharmacological interactions.

SECTION 8

Clinical Monitoring Framework

IGF-1: draw end of week 3 (peak exposure). Metabolic markers: start of clearance week.

Biomarker	Freq.	Target/Reference	Alert	Action
IGF-1	Q3m	Upper-normal for age; target 180-260 ng/mL	>300 ng/mL	Reduce to 1mg; >400: pause tesamorelin
HbA1c	Q3m	<5.7%	>6.0%	Increase imeglimin to 1000mg; review diet
Fasting glucose	Q3m	70-99 mg/dL	>110 mg/dL	Confirm with OGTT; same as HbA1c action
sjTREC (qPCR)	Q6m	Baseline; >25% rise at 12m	No rise at 12m	Check compliance; consider MRI
Naive CD4/CD8 (flow)	Q6m	Baseline; increase expected	Decline	Exclude illness; review rapamycin dose
CBC + differential	Q6m	WBC 4.5-11x10^9/L; lympho 20-40%	WBC <3.5 or lympho <15%	Pause rapamycin 4 wks; resume at 2.5mg
eGFR/creatinine	Q6m	eGFR >60	30-45: reduce imeglimin; <30: stop	Declining trend: nephrology referral
25-OH-D	Q6m	40-60 ng/mL	<30 or >80	Adjust D3 in 1000IU steps; recheck 8 wks
Thymic MRI	Annual	Baseline fat fraction; parenchyma increase	No change at 24m	Reassess adherence and protocol
DNAm clock (GrimAge)	Annual	Baseline; deceleration target	Acceleration	Review sleep, exercise, diet, stress

Table 17: Monitoring framework. Q3m=every 3 months; OGTT=oral glucose tolerance test.

SECTION 9

Evidence Quality Assessment (GRADE-informed)

High=consistent RCT; **Moderate**=RCT with limitations; **Low**=observational/animal; **Very Low**=in vitro/extrapolated.

Component	GRADE	Basis	Key Limitations
Tesamorelin (visceral fat)	High	Phase III CALM (n=403); CALM II; FDA approved	Approved indication is HIV lipodystrophy. Thymic: TRIIM n=9, open-label.
Thymosin a1 (immune)	Moderate	RCTs for HBV/HCV; meta-analyses for cancer adjuvant	No thymic regeneration RCT; benefit extrapolated from mechanism.
Rapamycin (longevity)	Moderate	ITP mouse data; PEARL 2025 (n=256, biomarkers)	No human survival RCT; transplant-to-longevity dose extrapolation.
Imeglimin (glucose)	Moderate	TIMES/TIMES-2 RCTs (n=536); Japan approved	Approved for T2D; thymic benefit is preclinical/mechanistic.
DHEA (thymic)	Low	TRIIM included (uncontrolled, n=9); DHEA-S/thymic correlation	No dedicated thymic RCT; TRIIM role cannot be isolated.
Zinc (thymulin)	Low-Mod	Deficiency causally linked to thymic atrophy; ZINCAGE RCT	Benefit clearest in deficient states.
Vitamin D3 (VDR)	Low-Mod	VDR on TECs established; AIRE upregulation in vitro	No thymic regeneration RCT; VDR/AIRE effects are in vitro.
Omega-3 (SASP)	Low-Mod	NF-kB/NLRP3 in RCTs; REDUCE-IT cardiovascular	No thymic-specific RCT; anti-SASP benefit inferred.
Melatonin (TEC)	Very Low	MT1/MT2 on TECs in rodent models	No human thymic evidence; all mechanistic data from mice.

Table 18: GRADE evidence quality. Green tint=High; red tint=Low or Very Low.

SECTION 10

Limitations & Regulatory Context

10.1 Evidentiary Limitations

No combined-protocol RCT. This 9-component protocol has never been tested as a combination. Evidence is drawn from separate studies in different populations. Additive or synergistic effects are inferred, not demonstrated.

Small TRIIM foundation. Primary human thymic regeneration evidence rests on a single open-label 9-person pilot. TRIIM-X (n=100, NCT04375774) is ongoing and will provide more robust evidence.

Age specificity. TRIIM enrolled adults 51-65; CALM enrolled HIV+ individuals. In younger adults (<35), GH axis dynamics and baseline IGF-1 differ. Dose calibration by IGF-1 monitoring is critical.

Fisetin removal (ITP null result). Fisetin removed based on NIA ITP null result for lifespan extension and emerging reagent quality concerns in the in vitro senolytic literature.

Long-term safety. No study has evaluated this combination beyond 2 years. Chronic GH/IGF-1 elevation carries theoretical cancer risk. Annual cancer screening should accompany protocols beyond 2 years.

10.2 Regulatory Context

Tesamorelin: FDA-approved (NDA 22-505). Off-label use legal with prescription. Not EMA-approved.

Thymosin a1: Approved >35 countries (Zadaxin). Not FDA-approved; research chemical in US.

Rapamycin: FDA-approved (Rapamune, NDA 21-083). Off-label longevity use requires prescription.

Imeglimin: Approved Japan (Twymeeg). Phase III ongoing US/EU. Off-label outside Japan.

SECTION 11

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