Thymic Rejuvenation Protocol

Strength Training Integration — Addendum

Supplement to: Thymic Rejuvenation Protocol — A Streamlined Evidence-Based Framework

Generated July 03, 2026

Purpose of this addendum. The 4-week thymopoiesis/clearance cycle described in the parent protocol is structurally identical to a classical undulating periodization model (3:1 loading-to-deload). This document provides the mechanistic rationale for synchronising progressive resistance training with the protocol phases. **No modifications to any drug dose, timing, or route of administration are required.**

§1 — The Shared Signalling Hub: $mTORC_1$

Both thymopoiesis and skeletal muscle protein synthesis (MPS) converge on the same intracellular node: mechanistic target of rapamycin complex 1 ($mTORC_1$). IGF-1 secreted in response to tesamorelin-driven GH binds the IGF-1 receptor and initiates a phosphorylation cascade (IRS-1 → PI3K → AKT) that activates $mTORC_1$. Downstream effectors S6K1 and 4EBP1 then drive ribosomal biogenesis for MPS in muscle and thymic epithelial cell (TEC) proliferation for thymopoiesis simultaneously. Rapamycin (FKBP12-mediated $mTORC_1$ inhibition) transiently attenuates both processes. The existing temporal separation of anabolic (weeks 1–3) and autophagic/clearance (week 4) phases is therefore simultaneously optimal for skeletal muscle and for the thymus.

Signal / Agent	Molecular Step	Direct Effect	Tissue Outcome
GH (from tesamorelin)	IGF-1R → IRS-1 → PI3K → AKT	$mTORC_1$ activation	MPS + TEC proliferation
$mTORC_1$ → S6K1	Phosphorylates rpS6, eIF4B	Ribosomal biogenesis	Myofibrillar protein synthesis ↑
$mTORC_1$ → 4EBP1	Releases eIF4E	Cap-dependent translation initiation	Satellite cell activation
Rapamycin (FKBP12)	Allosteric $mTORC_1$ inhibition	Autophagy induction	Senescent cell clearance + protein QC
AMPK (exercise + imeglimin)	Inhibits $mTORC_1$ via TSC2	Energy sensing / glucose uptake	GLUT4 translocation in myocytes

Table 1. Shared IGF-1 / $mTORC_1$ cascade with dual relevance to skeletal muscle and thymic epithelium. All five signals are active within the existing protocol.

> **Key insight:** The protocol requires no pharmacological modification to support resistance training. The anabolic window (weeks 1–3: elevated IGF-1, unblocked $mTORC_1$) and the clearance window (week 4: rapamycin-driven autophagy) are already optimally positioned — they serve a second biological purpose without any additional intervention.

§2 — The 4-Week Cycle as Undulating Periodization

The 3:1 loading-to-deload ratio in the thymic protocol is a recognised structure in evidence-based resistance training programming. Monthly undulating periodization (MUP) models — three progressive loading weeks followed by a planned deload — have been validated in meta-analyses as producing superior long-term hypertrophic and strength outcomes relative to uninterrupted linear loading. The mapping between thymic protocol phases and standard periodization phases is exact and requires no tracking overhead: week-of-cycle and training-phase are the same variable.

Week	Thymic Phase	Training Phase	Biological Rationale	Load Parameters
1	THYMOPOIESIS	Ramp	IGF-1 rising from tesamorelin restart; satellite cell activation; technique reinforcement after week 4 deload	65–75% 1RM; 3–4 sets; compound movements
2	THYMOPOIESIS	Peak Volume	IGF-1 at plateau; $mTORC_1$ fully unblocked; maximum MPS capacity window of the cycle	70–80% 1RM; highest set count (4–5 sets); hypertrophy rep range
3	THYMOPOIESIS	Peak Intensity	Capitalise on week 2 volumetric adaptation; peak neural drive + myofibrillar stimulus; PR window	80–90% 1RM; 3–4 sets; lower reps (3–6)
4	CLEARANCE	Deload	Rapamycin activates autophagy; protein QC; connective tissue recovery; supercompensation primed for week 1	≤50% of week 2 volume; 50–60% 1RM; avoid heavy compounds Mon–Thu

Table 2. Exact alignment of thymic protocol phases with undulating periodization training phases. 1RM = one-repetition maximum. Mon–Thu restriction in week 4 reflects rapamycin inhibition window (see §3).

> **Annual summary:** Over 12 months (13 complete 4-week cycles), the trainee accumulates 39 weeks of progressive loading and 13 planned deload weeks — a 3:1 ratio that most evidence-based programming guidelines recommend. This emerges directly from the thymic protocol structure with no additional planning burden.

§3 — Rapamycin Pharmacokinetics and the Training Window

Concern about rapamycin and muscle protein synthesis derives primarily from continuous infusion and frequent oral dosing studies. With once-monthly oral dosing at 5 mg, the pharmacokinetic (PK) profile creates a well-defined inhibition window occupying only the first four to five days of the seven-day deload week. Sirolimus (rapamycin) has a T_{max} of 1–3 h after oral tablet administration, oral bioavailability of approximately 14%, and a mean elimination half-life ($t_{1/2}$) of 57–63 h in healthy adults. After a single 5 mg fasted dose on Monday morning, meaningful $mTORC_1$ inhibition is predicted through Friday, with near-complete clearance by Sunday — before the week 1 ramp begins.

Day of Week 4	Rapamycin PK Status	Training Guidance
Monday (Day 0)	Dose day (5 mg, fasted). C_{max} reached ~2 h post-dose.	REST or light walk. No resistance training.
Tuesday (Day 1)	Near C_{max} → falling. ~1st $t_{1/2}$ elapsed overnight.	DELOAD only. Stretching, mobility, light bodyweight.
Wednesday (Day 2)	~1.0× $t_{1/2}$: ~50% cleared.	LIGHT session only. Avoid heavy compounds or eccentric loading.
Thursday (Day 3)	~1.4× $t_{1/2}$: ~62% cleared.	LIGHT cardio acceptable. Zone 2 aerobic fine. No maximal effort.
Friday (Day 4)	~2.0× $t_{1/2}$: ~75% cleared.	MODERATE session acceptable if desired. Light compounds, high reps.
Saturday (Day 5)	~3.0× $t_{1/2}$: ~87% cleared.	NORMAL training resumes. Week 1 ramp can begin Saturday if cycle starts here.
Sunday (Day 6)	~4.0× $t_{1/2}$: ~94% cleared. Negligible inhibition.	FULL week 1 loading. $mTORC_1$ essentially uninhibited.

Table 3. Day-by-day rapamycin PK status and recommended training approach during week 4. $t_{1/2} \approx 60$ h (single 5 mg oral dose). Clearance percentages assume first-order kinetics. Individual CYP3A4/P-gp variation may shift the window ±1–2 days.

Context: weekly vs. monthly rapamycin and MPS exposure. Drummond et al. (*J Physiol*, 2009) demonstrated ~50% blunting of post-exercise MPS under continuous rapamycin infusion. The longevity community's common weekly regimen (5 mg every 7 days, 52 doses/year) provides no sustained $mTORC_1$-free window. This protocol delivers 13 inhibitory episodes per year (one per 28-day cycle), each lasting ~4–5 days of meaningful inhibition. The remaining ~316 days per year are entirely rapamycin-free, providing a substantially more favourable MPS exposure profile than weekly dosing regimens.

§4 — Week-by-Week Training Parameters

The following table provides specific programming parameters for each week of the cycle. These are a framework; individual programmes should be adjusted for training history, recovery capacity, and HRV feedback. Any evidence-based resistance training system (powerlifting, bodybuilding, Olympic lifting) is compatible — only the load parameters and the week 4 rest constraint are prescribed here.

Parameter	Wk 1 — Ramp	Wk 2 — Volume	Wk 3 — Intensity	Wk 4 — Deload
Intensity (% 1RM)	65–75%	70–80%	80–90%	50–60%
Sets/muscle group/week	12–14	16–20	10–14	6–8
Rep range	8–12	8–15	3–6	12–15
Rest between sets	90–120 s	60–90 s	2–4 min	60–90 s
Session frequency	3–4×/wk	4–5×/wk	3–4×/wk	2–3×/wk
Movement emphasis	Compounds + accessories	High-volume compounds	Heavy compounds, minimal accessories	Mobility + light compound
Progress metric	Load ramp + technique	Volume accumulation	Load PRs	Recovery (HRV, soreness)
IGF-1 level	Rising ↑	Peak ↑↑	Peak sustained ↑↑	Falling (tesam. paused)
$mTORC_1$ status	Free	Free	Free	Inhibited Mon–Fri
Tesamorelin	Active	Active	Active	PAUSED
Rapamycin	None	None	None	5 mg oral, Monday fasted

Table 4. Week-by-week training parameters mapped to protocol phases. Sets per muscle group represent a moderate hypertrophy target; advanced trainees may use higher volumes. 1RM = one-repetition maximum.

Cardiorespiratory training

Aerobic training (Zone 2 cycling, swimming, rowing) does not activate $mTORC_1$ as its primary adaptation signal and is not meaningfully blunted by rapamycin. Zone 2 sessions can continue throughout week 4 without restriction. High-intensity interval training (HIIT) does engage $mTORC_1$ signalling for mitochondrial biogenesis and should be treated the same as resistance training — avoid Monday–Wednesday of week 4.

§5 — IGF-1 Direct Anabolic Effects on Skeletal Muscle

Tesamorelin-driven IGF-1 elevation exerts direct anabolic effects on skeletal muscle beyond its role as an $mTORC_1$ activator. The TRIIM trial (Fahy et al., *Aging Cell* 2019) noted lean mass preservation as a secondary finding at the modest IGF-1 elevations produced by the GH secretagogue regimen — likely reflecting IGF-1 anabolic activity on muscle as a pleotropic benefit. The mechanistic basis is multifactorial and acts across weeks 1–3 of every cycle.

IGF-1 / GH Action	Molecular Mechanism	Training Relevance
Satellite cell activation	IGF-1R → PI3K → AKT → CDK4/CDK6 → G_1/S cell cycle entry	Expanded myosatellite pool; more repair-capable cells post-eccentric loading
Myofibrillar MPS	AKT → $mTORC_1$ → S6K1 → rpS6 phosphorylation → ribosomal biogenesis	Direct amplification of the post-exercise MPS signal; synergistic with mechanical load
Anti-apoptotic signalling	AKT → phospho-Bad (Ser_{136}) → cytochrome c suppression	Reduced training-induced myocyte apoptosis; higher net cell survival after eccentric load
Glucose uptake	AKT → AS160 phosphorylation → GLUT4 vesicle translocation to sarcolemma	Improved intra-workout glucose availability; enhanced glycogen resynthesis post-session
Connective tissue remodelling	IGF-1R → MAPK/ERK → tenocyte and fibroblast proliferation; collagen synthesis ↑	Tendon and ligament adaptation to increasing training loads; reduced injury risk
GH direct effects (IGF-1-independent)	GH receptor → JAK2 → STAT5b → muscle-specific gene expression; lipolysis	Substrate partitioning toward lean mass; reduced intramuscular lipid accumulation

Table 5. Direct anabolic and structural effects of IGF-1/GH on skeletal muscle and connective tissue, active during weeks 1–3 of each cycle.

> **Evidence caveat:** Most mechanistic IGF-1/MPS data derives from in vitro studies, rodent models, or clinical populations (GH-deficient adults, HIV-associated wasting) receiving supraphysiological doses. Tesamorelin 2 mg SC targets upper-normal IGF-1 for age, not supraphysiological levels. Anabolic effects at this range are directionally supported but quantitatively uncertain in healthy young adults (see §8).

§6 — Supporting Stack Contributions to Training

Five components of the daily base stack carry independent evidence supporting resistance training performance and recovery. No dose modification is required; their training-relevant mechanisms are additive to the primary IGF-1/mTOR axis.

Component	Training-Relevant Mechanism	Training Benefit	Practical Note
DHEA (25–50 mg/day)	Peripheral conversion to testosterone via androstenedione; direct AR activation; adrenal precursor replenishment	Mild androgenic anabolic signal on top of IGF-1; supports satellite cell activation; magnitude modest at 25–50 mg in men aged 29 but directionally correct	Morning, away from tesamorelin
Imeglimin (500–1000 mg/day)	AMPK activation → GLUT4 translocation; mitochondrial complex I stabilisation; additive with exercise-induced AMPK signalling	Enhanced glucose uptake during training; offsets rapamycin-induced insulin resistance in week 4; supports mitochondrial biogenesis	With dinner; AMPK effect is not time-sensitive relative to training
Omega-3 EPA+DHA (2–3 g/day)	Membrane phospholipid incorporation → reduced pro-inflammatory eicosanoids; resolvin/protectin synthesis; $mTORC_1$-independent MPS augmentation	Reduced DOMS and systemic inflammation post-training; independent MPS augmentation (Smith et al. 2011, older adults); tendon and ligament health	With meals; no interaction with training timing
Melatonin (0.3 mg/night)	MT1/MT2 agonism → circadian phase-setting; GH pulse amplification via sleep architecture; direct antioxidant (radical scavenging)	Deep sleep architecture supports nocturnal GH pulsatility — the primary GH secretory mode that tesamorelin augments; sleep quality is the primary non-training recovery variable	30 min before sleep; 0.3 mg physiological dose; do not increase
Vitamin D3 (3000–5000 IU/day)	VDR activation in skeletal muscle → myosin heavy chain isoform expression; calcium handling; VDR-mediated testosterone biosynthesis regulation	VDR deficiency is associated with impaired muscle function and increased injury risk; 25-OH-D ≥40 ng/mL associated with improved power output in observational data	With fat-containing meal; maintain 25-OH-D 40–60 ng/mL

Table 6. Training-relevant mechanisms of base stack components. All components are present in the parent protocol; no dose modifications required.

§7 — Practical Monitoring Considerations

Glucose management during training

Three converging signals raise blood glucose during heavy resistance training in weeks 1–3: (1) tesamorelin-driven GH/IGF-1 stimulating hepatic glucose output and lipolysis, (2) sympathoadrenal catecholamine release during exercise driving hepatic glycogenolysis, and (3) transient post-exercise insulin resistance. Imeglimin's AMPK-mediated GLUT4 translocation partially counteracts all three. In a metabolically healthy individual, post-training glucose spikes of 140–180 mg/dL (7.8–10.0 mmol/L) are expected during weeks 1–3 and do not indicate pathology. During week 4, rapamycin additionally inhibits IRS-1 → PI3K insulin signalling; Imeglimin remains the primary buffer. If using a CGM, no protocol modification is indicated unless fasting glucose exceeds 100 mg/dL persistently or post-prandial glucose remains above 180 mg/dL for more than 2 hours.

Training timing relative to tesamorelin

Tesamorelin is administered SC at bedtime (~22:00–23:00) to coincide with the physiological nocturnal GH pulse. Afternoon resistance training sessions (14:00–18:00) are ideal: (a) circadian peak in muscle force output occurs in the afternoon in most individuals, (b) the ≥6-hour gap between training and tesamorelin injection allows the training stimulus to be delivered before the nocturnal GH/IGF-1 surge, extending the overnight anabolic window, and (c) GH secretagogue efficacy is maximised when injected during low serum glucose — avoid large carbohydrate meals within 2 hours before bedtime injection.

Protein intake

Standard evidence-based recommendations suggest 1.6–2.2 g/kg/day of total protein, distributed across ≥4 meals, with leucine-rich sources (whey, eggs, lean meat) prioritised post-workout to maximise leucine-sensing at $mTORC_1$. During weeks 1–3 the elevated IGF-1 context may amplify the leucine response; the upper range (2.0–2.2 g/kg/day) is advisable. During week 4 protein intake should be maintained despite attenuated MPS — amino acids are still required for autophagy-driven protein quality control and structural maintenance.

Monitoring additions for training integration

Biomarker	Frequency	Training Integration Note
IGF-1	Every 3 months (existing)	Draw end of week 3 (peak tesamorelin exposure); also functions as indirect anabolic readout for training adaptation context
HbA1c + fasting glucose	Every 3 months (existing)	Training-driven glucose variability is transient; persistent HbA1c ≥5.8% warrants review of tesamorelin + rapamycin + training combination
Testosterone (free + total)	Every 6 months (add)	Baseline and protocol response; DHEA conversion context; relevant if training load is high and recovery is impaired

Biomarker	Frequency	Training Integration Note
DEXA body composition	Every 6 months (add)	Primary objective lean-mass outcome measure; preferable to body weight; segment lean mass and fat mass separately
HRV (wearable, daily)	Daily, continuous (add)	Primary within-cycle feedback variable; expect high at week 1 start, declining through week 3, recovering in week 4; persistently low HRV at week 3 end indicates accumulated fatigue — reduce intensity or extend deload
Creatine kinase (CK)	Week 3 peak, optional	Training-induced muscle damage marker; elevated CK (≥1000 U/L) after week 3 peak confirms adequate eccentric stimulus; extreme elevation (>5000 U/L) suggests overreach — extend deload

Table 7. Monitoring additions for strength training integration. Items marked 'existing' are already in the parent protocol monitoring panel.

§8 — Limitations and Evidence Quality

#	Limitation	Description	GRADE
1	No combined RCT evidence	No randomised controlled trial has combined GH secretagogues with structured resistance training periodization in healthy young adults. The mechanistic rationale is strong, but the combined protocol is experimentally untested.	Very Low
2	IGF-1 dose-response uncertainty	Most IGF-1/MPS interaction data uses supraphysiological IGF-1 (recombinant infusion, acromegaly populations). At upper-normal IGF-1 from tesamorelin 2 mg, the magnitude of anabolic amplification in a healthy 29-year-old is unknown.	Low (indirect, heterogeneous populations)
3	Rapamycin training window: extrapolated PK	Week 4 training guidance is based on first-order PK modelling. Individual CYP3A4/P-gp metaboliser status shifts rapamycin $t_{1/2}$ from 40–90+ h. Sirolimus TDM (trough level at Day 4 post-dose) would quantify this uncertainty.	Moderate (PK) / Low (training translation)
4	Periodization-IGF-1 interaction	Meta-analytic support for 3:1 MUP comes from drug-free recreationally trained subjects. The interaction with exogenous IGF-1 elevation during loading phases is uncharacterised.	Low
5	DHEA anabolic effect modest at age 29	DHEA androgenic conversion is most meaningful in populations with reduced adrenal reserve (age 40+). At age 29, endogenous testosterone is likely optimal; DHEA primarily serves thymic and non-androgenic functions in this protocol.	Low for anabolic training benefit in young healthy males

Table 8. Evidence limitations for the strength training integration component. GRADE = Grading of Recommendations Assessment, Development and Evaluation.

References

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