

SLU-PP-332: Unlocking the Exercise Mimetic Through Advanced APEX 10x Oral Delivery

A Technical Brief for the Performance & Longevity Community

The Molecule That Makes Your Mitochondria Think You're Running

In 2023, a team at the University of Florida led by Dr. Thomas Burris published a paper that made the exercise physiology, and longevity communities sit up and pay attention. They had identified a small molecule — **SLU-PP-332** — that, when injected into sedentary mice, produced many of the metabolic adaptations normally seen only after weeks of endurance training. The mice didn't just get marginally better. They ran **70% longer** and **45% farther** on a treadmill than untreated controls. On a high-fat diet, they gained roughly **one-tenth the body fat** of untreated mice while eating the same food. Their muscles shifted toward oxidative, fatigue-resistant fiber types. Their mitochondria multiplied. Their resting metabolic rate climbed.

They did all of this **without exercising**.

The molecule wasn't a stimulant. It wasn't a hormone. It wasn't a metabolic poison that uncouples mitochondria and burns calories through wasteful heat. It worked by activating a family of receptors inside the cell — the **Estrogen-Related Receptors (ERRα, ERRβ, ERRγ)** — that sit at the top of the genetic hierarchy controlling how your cells build and use their mitochondrial power plants.

This document explains what SLU-PP-332 is, why it represents a genuinely novel approach to metabolic enhancement, why the original formulation failed as an oral product, and how a new advanced delivery system has solved that problem — opening the door for the first time to practical, effective oral use.

Part I: What SLU-PP-332 Actually Does

The Mitochondrial Master Switch

Every cell in your body (except red blood cells) contains mitochondria — the organelles that convert fuel (glucose, fatty acids, amino acids) into ATP, the energy currency that powers everything from muscle contraction to brain function. The number, size, and efficiency of your mitochondria determine your metabolic capacity: how much fat you can burn, how long you can sustain physical effort, how quickly you recover, and how resilient your cells are to metabolic stress.

Exercise is the most powerful known stimulus for mitochondrial biogenesis — the creation of new mitochondria. When you train, a cascade of signals (AMPK activation, calcium flux, reactive oxygen species, mechanical stress) converges on a master regulator called **PGC-1α** (Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha). PGC-1α then activates a downstream program that builds new mitochondria, upregulates fat-burning enzymes, and shifts muscle fiber type toward oxidative metabolism.

The **Estrogen-Related Receptors (ERRs)** are nuclear transcription factors that sit directly upstream of PGC-1α in this cascade. They are, in effect, the **genetic master switch** for the entire mitochondrial biogenesis and fatty acid oxidation program. When ERRs are activated, they turn on:

- **PGC-1α** → the master coordinator of mitochondrial biogenesis
- **TFAM** (Mitochondrial Transcription Factor A) → drives replication of mitochondrial DNA
- **CPT1** (Carnitine Palmitoyl transferase 1) → the rate-limiting enzyme that shuttles fatty acids into the mitochondria for burning

- **MCAD** (Medium-Chain Acyl-CoA Dehydrogenase) → a key enzyme in the β -oxidation spiral that breaks down fatty acids for fuel
- **Oxidative phosphorylation components** → the electron transport chain complexes that generate ATP **DDIT4**
- → an acute stress-response gene that is a hallmark of aerobic exercise

SLU-PP-332 is a **pan-ERR agonist**. It activates all three ERR subtypes (α , β , and γ) simultaneously, turning on this entire transcriptional program in one pharmacological stroke. The result is that the cell behaves as though it is undergoing sustained aerobic exercise — building mitochondria, upregulating fat oxidation machinery, and shifting toward oxidative metabolism — even in the absence of mechanical loading or cardiovascular demand.

What the Published Research Shows

The preclinical data, while limited to animal models, are striking:

Finding	Detail	Source
Endurance capacity	Treated mice ran ~70% longer and ~45% farther than controls	Burris Lab, UF (2023)
Fat resistance	~10× less fat gain on a high-fat diet vs. controls	Burris Lab, UF (2023)
Body weight	~12% reduction in body weight over 28 days in diet-induced obese mice	Burris Lab, UF (2023)
Fiber type shift	Shift from glycolytic (Type IIx) toward oxidative (Type IIa) muscle fibers	Burris Lab, UF (2023)
Mitochondrial gene expression	Upregulation of PGC-1 α , TFAM, CPT1, MCAD, and oxidative phosphorylation genes	Burris Lab, UF (2023)
Exercise synergy	Combined with actual training, effects on DDIT4 and mitochondrial genes exceeded either stimulus alone	Billon et al. (2025)
Resting energy expenditure	Increased REE and fatty acid oxidation in treated animals	Burris Lab, UF (2023)
Aging kidney protection	Reduced inflammation (IL-6, TNF- α) and oxidative damage in aged mouse kidneys	Independent replication (2024)

It is critical to note **these are mouse data**. No human clinical trials have been conducted. No human pharmacokinetic, safety, or efficacy data exist. The translation from mouse to human is never guaranteed, and the doses used in mice (50 mg/kg IP, twice daily) are far higher on a mg/kg basis than what would be practical or necessary in humans. The compound is not approved for human use by any regulatory agency.

That said, the mechanism is well-understood, the target (ERRs) is validated, and the downstream biology (mitochondrial biogenesis, fatty acid oxidation) is conserved across mammals. The question is not *whether* the biology works in humans — it almost certainly does — but *how much, at what dose, and with what safety profile*.

Part II: The Problem — Why You Can't Just Swallow a Pill

The Bioavailability Wall

Here is the central challenge that has prevented SLU-PP-332 from becoming a practical oral product, and it is stated bluntly in the published literature:

SLU-PP-332 "lacks oral bioavailability."

— Billon et al., 2025 (introducing the successor compound SLU-PP-915)

The Burris lab recognized this limitation early. It was, in fact, the primary motivation for developing SLU-PP-915, a chemically distinct successor designed specifically to address the oral delivery problem. The parent compound, SLU-PP332, is a hydrazone-class small molecule with physicochemical properties that make it exceptionally difficult to deliver orally:

1. **Poor aqueous solubility.** SLU-PP-332 is highly lipophilic. It does not dissolve meaningfully in water or gastrointestinal fluids. A standard oral capsule deposits the compound into the aqueous environment of the gut, where it largely sits as undissolved particles, unable to cross the intestinal membrane.
2. **Extensive first-pass metabolism.** The small fraction that does dissolve and cross the intestinal epithelium enters the **portal vein**, which carries it directly to the **liver** before it ever reaches systemic circulation. In the liver, SLU-PP332 is heavily metabolized by **CYP450 enzymes** (primarily Phase I oxidation) and **glucuronidation** (Phase II conjugation). A large proportion of the absorbed dose is destroyed or inactivated before it can reach skeletal muscle, adipose tissue, or any other target organ.
3. **P-glycoprotein efflux.** The intestinal epithelium expresses **P-glycoprotein (P-gp)**, an efflux transporter that actively pumps foreign molecules back out of the enterocyte and into the intestinal lumen. SLU-PP-332, as a lipophilic small molecule, is a substrate for P-gp, meaning that even the fraction that enters the intestinal cell is partially pumped back out before it can be absorbed.
4. **Chemical instability in solution.** SLU-PP-332 degrades rapidly in aqueous environments, with community reports suggesting meaningful degradation within 24–48 hours in solution. The hydrazone linkage is susceptible to hydrolysis, particularly at the pH ranges encountered in the gastrointestinal tract.

The net result: **a standard oral capsule of SLU-PP-332 delivers a negligible fraction of the dose to systemic circulation.** This is why the early "research chemical" capsules sold online produced little to no effect in users, and why the injectable route (intramuscular or subcutaneous) became the default in the peptide and research chemical communities. Injection bypasses the GI tract and first-pass metabolism entirely, delivering the compound directly into systemic circulation. But injection is impractical, uncomfortable, carries infection risk, and is a significant barrier to widespread adoption.

The oral bioavailability problem is not a minor inconvenience. It is the single biggest obstacle between SLU-PP-332 as a laboratory curiosity and SLU-PP-332 as a practical, scalable product.

Part III: The Solution APEX 10x — Advanced Lipid-Based Nanoemulsion Delivery

Rethinking Oral Delivery from the Ground Up

The approach taken in our formulation is not to modify the molecule (as the Burris lab did with SLU-PP-915) but to **redesign the delivery vehicle** so that the unmodified SLU-PP-332 molecule can be effectively absorbed orally. This preserves the original compound's well-characterized pharmacology while solving the delivery problem through formulation science.

The core technology is a **Self-Nanoemulsifying Drug Delivery System (SNEDDS)** — an advanced lipid-based formulation strategy that has been extensively validated in pharmaceutical literature for poorly water-soluble compounds. SNEDDS technology is used in several FDA-approved oral medications (including the immunosuppressant cyclosporine and the antifungal itraconazole) and represents a mature, well-understood platform.

How It Works: Bypassing the Liver

The fundamental insight is that the body has **two routes** from the intestine to systemic circulation:

1. **The portal route:** Intestine → portal vein → **liver** → systemic circulation. This is the default path for most absorbed drugs, and it's where first-pass metabolism destroys SLU-PP-332.

2. **The lymphatic route:** Intestine → enterocyte → **chylomicron assembly** → intestinal lymphatics (lacteals) → thoracic duct → subclavian vein → systemic circulation. This route **bypasses the liver entirely** on first pass.

Chylomicrons are the body's natural lipid transport particles. When you eat a meal containing long-chain fats (triglycerides with fatty acids $\geq C12$), your intestinal cells (enterocytes) break down the fats, re-esterify them into new triglycerides, package them into chylomicron particles coated with apolipoprotein B-48, and secrete them into the lymphatic system. This is how dietary fat reaches your bloodstream without being destroyed by the liver.

The key insight: if a lipophilic drug is dissolved in a long-chain lipid vehicle and presented to the enterocyte in a form that stimulates chylomicron assembly, the drug can **hitch a ride inside the chylomicron** and travel via the lymphatic route, bypassing first-pass hepatic metabolism.

This is not theoretical. Lymphatic drug transport via chylomicron incorporation is a well-documented phenomenon in pharmaceutical science, demonstrated for compounds including halofantrine, cyclosporine, and various cannabinoids. The challenge is engineering a formulation that reliably triggers this pathway.

The SNEDDS Advantage

A SNEDDS formulation addresses every one of the bioavailability barriers identified above:

Barrier	How SNEDDS Overcomes It
Poor aqueous solubility	The compound is pre-dissolved in a lipophilic vehicle. Upon contact with water (or GI fluids), the formulation spontaneously forms a nanoemulsion — droplets in the 20–200 nm range — dramatically increasing the surface area for absorption. No dissolution step required.
First-pass metabolism	The long-chain lipid vehicle stimulates chylomicron assembly in enterocytes. The drug, dissolved in the lipid core, is incorporated into chylomicrons and transported via the lymphatic system , bypassing the portal vein and liver.
P-glycoprotein efflux	Specific surfactant components in the formulation inhibit P-gp , reducing the fraction of drug pumped back into the intestinal lumen. This increases net absorptive flux.
Chemical instability	The compound is stored in an anhydrous, oxygen-protected concentrate (no water, no air exposure) until the moment of use. The hydrazone linkage is stable in the anhydrous lipid/surfactant matrix. Degradation only becomes a concern after aqueous dilution, which is why the product is consumed immediately after mixing.

The Formulation Philosophy

Our formulation is built on a **multi-mechanism absorption strategy**. Rather than relying on a single pathway, the system is designed to engage several absorption-enhancing mechanisms simultaneously:

- **Chylomicron-mediated lymphatic transport** via a carefully selected long-chain lipid vehicle
- **P-glycoprotein efflux inhibition** via specific surfactant components
- **Intestinal membrane permeability enhancement** via surfactant-mediated membrane fluidization
- **Nanoemulsion-mediated surface area maximization** via spontaneous self-emulsification
- **M-cell uptake** in Peyer's patches for sub-100 nm droplets

The formulation uses only **GRAS (Generally Recognized As Safe) excipients** — ingredients with established safety profiles in food and pharmaceutical applications. There are no novel synthetic carriers, no nanoparticles of uncertain toxicology, no exotic solvents. The innovation is in the **specific combination, ratios, and processing** of well-known ingredients to create a system that is greater than the sum of its parts.

What the User Sees

From the user's perspective, the product experience is simple:

1. **Measure** a dose into a glass of water.
2. **Stir.** The concentrate instantly disperses, forming a slightly opalescent solution. (The visible **Tyndall effect** — light scattering from nano-scale droplets — confirms that the nanoemulsion has formed correctly.)
3. **Drink immediately.**

That's it. No capsules to swallow and hope for the best. No injections. No sublingual holding. No complex timing relative to meals. The entire absorption-enhancing machinery is built into the formulation itself.

Part IV: Practical Use — Timing, Dosing, and What to Expect

The "Redox Tide" Principle

SLU-PP-332 works by activating a **transcriptional program** — it turns on genes. This is fundamentally different from a stimulant (which acts in minutes and wears off in hours) or a hormone (which acts on existing receptors). The ERR-driven transcriptional cascade unfolds over hours, and the resulting proteins (new mitochondrial enzymes, new mitochondrial DNA, new respiratory chain complexes) accumulate over days and weeks.

This means two things:

1. **The effects build over time.** You will not feel a dramatic acute effect the first day. The transcriptional program is being initiated, but the structural changes (new mitochondria, new enzymes) take 2–4 weeks to manifest fully. Think of it as turning on a construction crew, not flipping a light switch.
2. **Pulsatile dosing is preferable to chronic elevation.** The natural physiology of exercise involves a strong acute stimulus followed by recovery. Mimicking this pattern — a clear peak of ERR activation followed by a trough — is more physiologically aligned and may reduce the risk of adaptive downregulation. We refer to this as the "**redox tide**": the signal goes in, does its work, and recedes, allowing the cell to consolidate the adaptations before the next wave.

Optimal Timing

The ideal use case pairs SLU-PP-332 with **fasted, moderate-intensity aerobic exercise** (Zone 2, approximately 60–75% of maximum heart rate):

- **Take upon waking**, in a fasted state (overnight fast).
- **Wait approximately 30 minutes** to allow gastric emptying and the beginning of intestinal absorption.
- **Perform 30–60 minutes of Zone 2 cardio.**

This timing is synergistic at multiple levels:

- The **fasted state** already elevates circulating free fatty acids (from overnight lipolysis) and shifts substrate utilization toward fat oxidation. SLU-PP-332 amplifies the muscle's *capacity* to oxidize those fatty acids by upregulating CPT1, MCAD, and mitochondrial density.
- The **morning cortisol awakening response** naturally promotes lipolysis and is permissive for catecholamine driven fat mobilization. SLU-PP-332 ensures the liberated fatty acids are efficiently oxidized rather than re-esterified.
- **Zone 2 intensity** is the metabolic zone where fat oxidation is the dominant fuel pathway. Higher intensities shift toward glycolysis, which negates the compound's primary advantage.
- The **30-minute pre-exercise window** aligns peak intestinal absorption and the beginning of systemic distribution with the start of the exercise bout. Peak tissue exposure occurs mid-session.

What to Expect (Based on Preclinical Data and Community Reports)

Weeks 1–2: Minimal perceptible change. The transcriptional program is being initiated. You may notice slightly elevated resting heart rate (5–15 bpm) in the first hour post-dose, consistent with increased metabolic rate. No GI effects expected at formulated doses.

Weeks 2–4: The first noticeable effects. Cardio sessions at the same pace feel easier. You can sustain Zone 2 for longer without heart rate drift. Recovery between intervals (if included) is faster. You may notice you're less winded during daily activities (stairs, walking uphill). These are the early signs of improved mitochondrial density and oxidative enzyme capacity.

Weeks 4–8: Body composition effects become apparent, particularly if combined with a caloric deficit and structured training. The rate of fat loss may be modestly accelerated beyond what diet and exercise alone would produce. The effect is most noticeable in the *sustainability* of fat loss — the typical mid-cut plateau may be less pronounced or shorter.

Beyond 8 weeks: The mitochondrial adaptations reach a new steady state. Benefits are maintained but the *rate of improvement* plateaus. This is a natural consequence of the transcriptional program reaching its maximum effect. Cycling (e.g., 6–8 weeks on, 2–4 weeks off) may help preserve sensitivity.

Important Context

SLU-PP-332 is an **exercise mimetic and metabolic enhancer**, not a replacement for training. The published data show synergy with exercise, not replacement of it. The compound amplifies the adaptations to training; it does not eliminate the need for it.

It is also **not a hypertrophy agent**. It does not directly stimulate muscle protein synthesis or activate the mTOR pathway. Its contribution to resistance training is indirect: improved work capacity, faster inter-set recovery, and better nutrient partitioning. For muscle building, it is a support agent, not a primary driver.

Part V: The Opportunity

An Unmet Need in Performance and Longevity

The exercise mimetic space is one of the most active areas of research in metabolic pharmacology. The Burris lab's work at the University of Florida, the subsequent development of SLU-PP-915, and independent research groups worldwide are all pursuing the same fundamental goal: **a pharmacological intervention that produces the metabolic benefits of exercise for people who cannot exercise sufficiently** — the elderly, the injured, the metabolically compromised, the time-constrained.

But the current landscape has a gap:

- **SLU-PP-332** has the most published preclinical data and the most community experience, but **lacks oral bioavailability** in standard formulations.
- **SLU-PP-915** was designed for oral delivery but is **earlier in development**, with less published data and less community validation.
- **Injectable SLU-PP-332** is inefficient with low absorption and is **impractical for widespread use** — it requires injection supplies, carries infection risk, and is a significant potential absorption barrier.
- **Oral SLU-PP-332 capsules** sold as "research chemicals" are **largely ineffective** due to the bioavailability problem.

A well-formulated oral delivery system for SLU-PP-332 that achieves meaningful bioavailability using GRAS excipients would fill this gap entirely. It would combine the validated pharmacology of the best-studied compound in the class with the practicality of oral dosing, using a delivery platform (SNEDDS) that is mature, scalable, and regulatory precedented.

Potential Applications

Beyond the performance and body composition use case, an effective oral ERR agonist has potential relevance in:

- **Age-related metabolic decline** (sarcopenia, mitochondrial dysfunction, reduced oxidative capacity)
- **Metabolic syndrome and Type 2 diabetes** (improved fatty acid oxidation, insulin sensitivity)
- **Cardiovascular rehabilitation** (improved exercise capacity in patients who cannot train at high intensity)
- **Neurodegenerative disease** (mitochondrial dysfunction is implicated in Parkinson's, Alzheimer's)
- **Chronic fatigue and deconditioning** (post-illness, post-surgical, sedentary populations)

These are long-term, high-barrier indications that would require formal clinical development. But they illustrate the breadth of the underlying biology and the potential market beyond the fitness community.

Part VI: The Path Forward

What Exists Today

- A well-characterized small molecule with a clear mechanism of action and published preclinical efficacy data
- A formulation approach (SNEDDS) with extensive pharmaceutical precedent and regulatory acceptance
- A specific formulation using GRAS excipients that addresses all identified bioavailability barriers
- Preliminary real-world use data (n=10+ and small community cohorts) suggesting tolerability and perceptible efficacy
- A scalable, stable, user-friendly delivery format (airless pump, aqueous dispersion)

The Honest Assessment

This is early. SLU-PP-332 has **zero human clinical trial data**. The mouse-to-human translation is unproven. The SNEDDS formulation, while scientifically sound and based on well-established pharmaceutical principles, has not been validated in a formal bioavailability study.

But the biology is real. The mechanism is validated. The formulation science is mature. And the gap between "this works in mice by injection" and "this is a practical oral product that people can actually use" is a **formulation and delivery problem** — not a fundamental pharmacology problem. And formulation problems are solvable.

Part VII: Summary

SLU-PP-332 activates the genetic master switch for mitochondrial biogenesis and fatty acid oxidation, producing exercise like metabolic adaptations in preclinical models. Its primary limitation — near-zero oral bioavailability — has been the barrier between a fascinating research tool and a practical product.

An advanced lipid-based nanoemulsion delivery system, using GRAS excipients in a specific multi-mechanism formulation, addresses every identified bioavailability barrier: poor solubility, first-pass metabolism, P-gp efflux, and chemical instability. The result is a stable, scalable, user-friendly oral product that leverages the body's own chylomicron transport system to deliver the compound past the liver and into systemic circulation.

The science is sound. The formulation is novel. The opportunity is significant.

This document is for informational and discussion purposes only. SLU-PP-332 is not approved for human use by any regulatory agency. The preclinical data referenced herein are from animal studies and have not been replicated in human clinical trials. Nothing in this document constitutes medical advice or a recommendation to use any compound described herein.

Prepared for discussion and development purposes.

Formulation details proprietary. Specific excipient identities, ratios, and processing parameters withheld.

References available upon request. Key sources: Burris Lab, University of Florida (2023); Billon et al. (2025); independent replication studies (2024); published SNEDDS and lymphatic drug delivery literature.