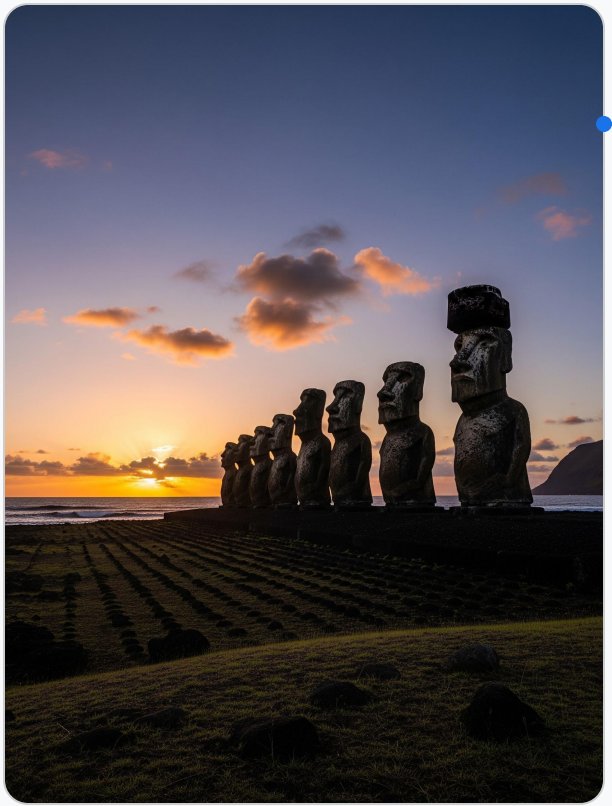
From Easter Island to Global Longevity: The Discovery of Rapamycin



Origins: Rapa Nui (1964)

Discovered in a soil sample from Easter Island, the compound was produced by the bacterium *Streptomyces hygroscopicus*. Originally studied as an antifungal, it was named "Rapamycin" after the island's native name.

The Universal Lifespan Extender

Rapamycin has become the "gold standard" in aging research, demonstrating lifespan extension across a vast evolutionary spectrum:

- **Yeasts:** Increased lifespan by mimicking caloric restriction.
- **C. Elegans:** Extended survival in nematodes via mTOR inhibition.
- **Drosophila:** Significant extension in fruit fly longevity.
- **Mice:** First mammal to show benefits, even when started late in life.
- **Marmosets (2024):** Recent breakthrough proving healthspan benefits in primates.

Rapamycin Lifespan Extension in Mice: Timing & Combinations

Very Early (Short)
♀ 10%
♂ 12%

Early in Life
♀ 18-26%
♂ 11-13%

Early + Metformin
♀ 23%
♂ 17%

Early + Acarbose
♀ 28%
♂ 22%

Later in Life
♀ 7-15%
♂ 12-18%

Later + Acarbose
♀ 28%
♂ 14%



Note: Data based on Median Lifespan increases. Rapamycin administration remains effective even when started at 19-20 months of age in mice.

Females Males

Rapamycin Lifespan Extension: Median vs. Max Lifespan Increases

Very Early (Short)
Median: ♀ 10% | ♂ 12%
Max: ♀ 0% | ♂ 12%

Early in Life
Median: ♀ 18-26% | ♂ 11-13%
Max: ♀ 23% | ♂ 8-16%

Early + Metformin
Median: ♀ 23% | ♂ 17%
Max: ♀ 17% | ♂ 24%

Early + Acarbose
Median: ♀ 28% | ♂ 22%
Max: ♀ 17% | ♂ 24%

Later in Life
Median: ♀ 7-15% | ♂ 12-18%
Max: ♀ 9-11% | ♂ 9%

Later + Acarbose
Median: ♀ 28% | ♂ 14%
Max: ♀ 12-18% | ♂ 18%



Note: Comparisons based on median vs maximum lifespan. Rapamycin remains effective even when administration starts at 19-20 months of age in mice.

● Females ● Males

Rapamycin: Activating Cellular Repair & Longevity

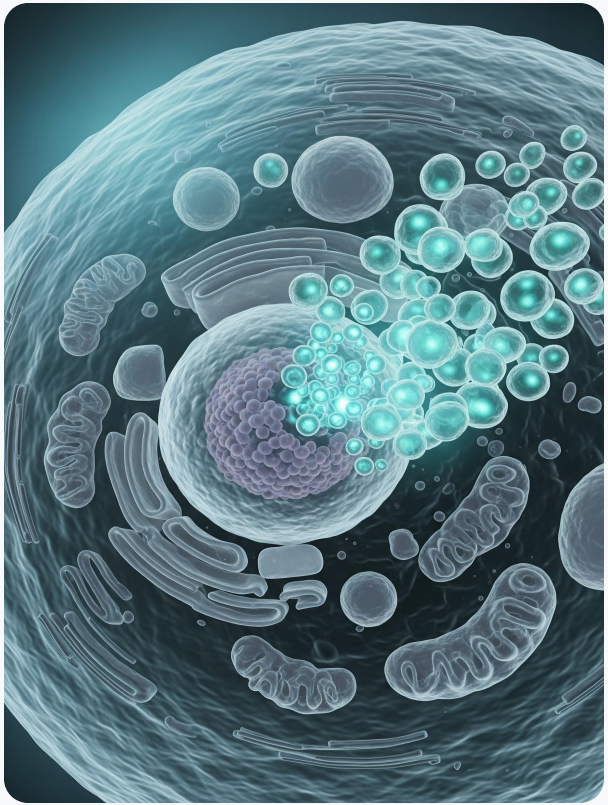
Mechanism of Action: Switching on Autophagy

In adversity (e.g. starvation), mTOR is switched off to prioritize cellular maintenance. Rapamycin mimics this state by blocking mTORC1:

- **Promotes Autophagy:** Efficient recycling of used cell molecules to slow aging.
- **Reduces Senescent Cells:** Eliminates "zombie" cells that drive inflammation.
- **Activates Nrf2:** Triggers a powerful internal antioxidant pathway.
- **DNA Resilience:** Enhances damage repair and reduces "immune exhaustion."

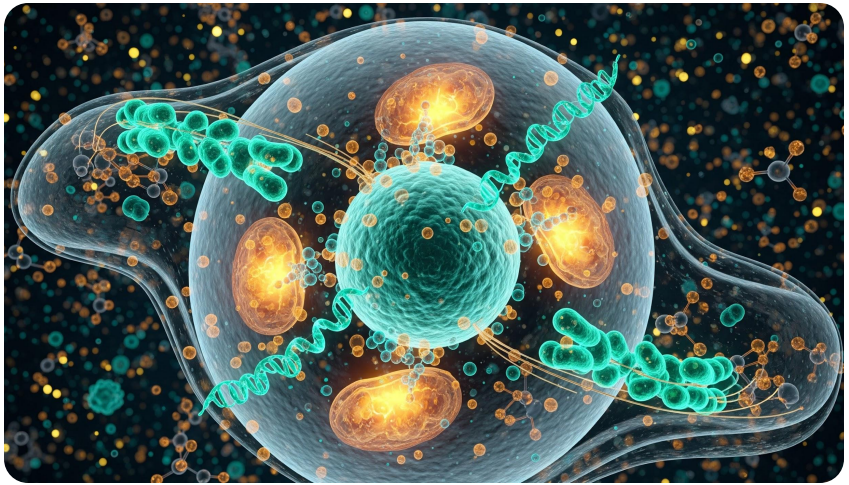
Strategies for Switching Off mTORC1 in Mice

- Caloric Restriction
- Rapamycin (Rapalogs)
- Rapa + Metformin
- Rapa + Acarbose
- Interleukin-11 Blocker



mTORC1: Nutrient Sensing and Cellular Decision Making

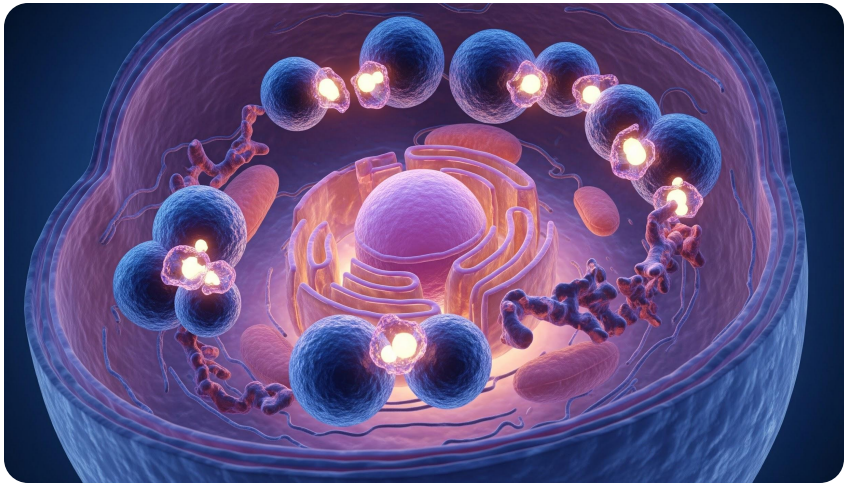
1. Nutrient Rich Conditions



mTORC1 is ACTIVE

- Fosters protein synthesis and cell growth
- Promotes cell multiplication (proliferation)
- Inhibits cellular maintenance pathways

2. Starvation or Rapamycin



mTORC1 is BLOCKED

- Switches on Autophagy (Cell Repair Mode)
- Recycles used cell molecules for efficiency
- Enhances cell protection and longevity

Rapamycin: Breakthrough Longevity in Aging Models

Lifespan Extension in Old Age

Rapamycin increases lifespan even when administered to 19-month-old (very old) mice. It is **as effective late in life** as when started earlier.

A 3-month high-dose treatment in 20-month-old mice resulted in a **dramatic increase in lifespan**.

Note: Effects persist after treatment; continuous dosing is not always required.

Broad Anti-Aging Impact

- **Cancer & Cardiac:** Reduces incidence and improves heart function.
- **Brain Health:** Combats vascular aging and neurodegeneration.
- **Reproduction:** Preserves ovarian function and delays menopause.
- **Cell Health:** Attenuates cell senescence across multiple types.

Conclusion

Rapamycin appears to have an anti-aging impact on a large number of disease-related processes in mice.

It is the first drug shown to have definitive anti-aging actions in a mammal.



Marmoset Study 2024: Healthspan and Lifespan Extension

Key Findings in Primates (Marmosets)

The 2024 study is the first to demonstrate both healthspan and lifespan extension in primates using Rapamycin:

- **Proteostasis Maintenance:** Sustained health of essential proteins over time.
- **First in Primates:** Bridging the gap between rodent studies and human potential.
- **Consistent Results:** Mirrors benefits seen in yeast, worms, and mice.



UT Health | Barshop Institute San Antonio

Adam B. Salmon, PhD Interview

The Marmoset Longevity Study with Rapamycin

Adam B. Salmon, PhD

UT Health San Antonio | Barshop Institute

"The Marmoset Longevity Interview with Rapamycin"

Comparative Lifespan Impact

YEAST: 60% strain increase in lifespan via Rapamycin.

WORMS: Lived at least 5 days longer than 25-day average.

FRUIT FLIES: Lived 10% longer with Rapamycin compound.

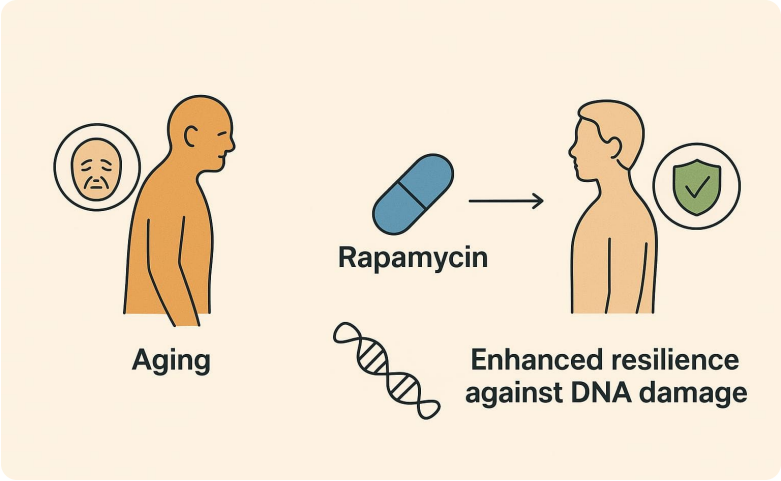
MICE: Males fed at age 19mo lived 9% longer than control.

DOGS: Improved cardiac function in older pilot study dogs.

PEOPLE: Elderly volunteers showed enhanced flu vaccine response.

Rapamycin: Geroprotective Effects on the Immune System

Source: BioRxiv Study (2025) - DNA Damage Resilience



Key Mechanism: DNA Damage Protection

DNA damage drives **immunosenescence**, accelerating whole-body ageing.

Immune ageing is fundamentally linked to DNA damage paired with **mTOR hyperactivation**.

"Genoprotective" Effect

Rapamycin directly lowers the DNA lesion burden, protecting immune cells from damage.

- **Reduced Senescence:** Significantly decreased **p21 markers** (DNA damage-induced senescence) compared to placebo.
- **Reversed Exhaustion:** Lowered immune exhaustion markers (**KLRG1, LAG3, NKG2A**).
- **Safe Modulation:** Achieved these benefits **without immunosuppression**.

Note: Rapamycin enhances resilience by resetting immune machinery.

Thymic Regeneration & Immune Reset

Study Focus: Short-term rapamycin administration in female mice



Resetting the Immune Machinery

mTOR inhibitors go beyond slowing aging—they reset parts of the body's immune system to a more youthful state.

Key Result: +30% Size Increase

The thymus bounced back, exceeding its original size after rapamycin treatment.

Cellular Improvements:

- **Renewed Organization:** Improved cellular structure within the regenerating glands.
- **Telomere Length:** Significant lengthening of thymocyte telomeres.
- **T Cell Restoration:** Restored populations of double-positive and CD8-single-positive T cells.

Source: ScienceDirect - pii/S0014299925007149

RAPAMYCIN: New Mechanism & Clinical Pearls

May 2026 Medical Update

1. Restoring ULK1 Activity

A landmark study in *Cell Metabolism* clarifies that low-dose pulsed Rapamycin specifically restores **ULK1 complex** activity.

Mitophagy & Cleanup

Selectively clears damaged mitochondria in cardiomyocytes and neurons, reducing lipofuscin accumulation by **22%**.

NEURO & CARDIOPROTECTIVE

2. Clinical Pearl (Attia/Huberman)

Rapamycin's benefit is highly dependent on **baseline protein intake**.

RISK **Sarcopenia:** Inhibiting mTOR while protein-restricted may lead to muscle loss.

SOLUTION**HLRT Stacking:** High-leucine resistance training preserves lean mass while maintaining cleanup.
Strategy: Separate windows of mTOR inhibition and amino acid activation.

Source: Cell Metabolism Study & Expert Consensus (Attia/Huberman 2026)

High-Leucine Resistance Training (HLRT)

Clinical strategy to overcome Anabolic Resistance • May 2026 update

1. The Leucine Threshold

Patients over 50 require a **bolus** of Leucine to "flip the switch" on the mTORC1 pathway.

The Threshold:
2.5g – 3.5g per meal

The Problem:
Standard meals only provide ~1g. Sessions are "wasted" without hitting the threshold.

2. The HLRT Protocol

- **Pre-Exertion:** 3–5g L-Leucine 30 mins **prior**.
- **Mechanical Tension:** Progressive overload (>70% 1-RM) to sensitize mTOR.
- **Post-Workout:** Second "Leucine hit" (3g+) within 60 mins.

3. Rapamycin Strategy

Because Rapamycin inhibits mTOR, clinicians use HLRT to **separate windows of inhibition and activation**.

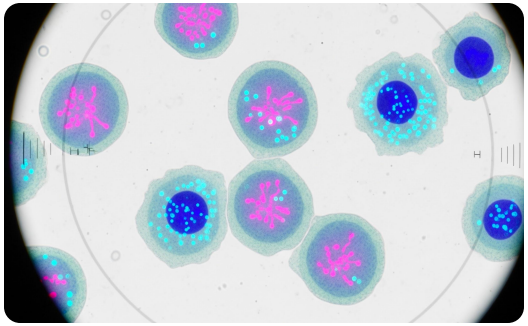
Anabolic Window:
Maximize synergy between mechanical load and nutrient signaling.

© 2026 Clinical Training Standards • Anabolic Resistance Clinical Update

Evidence Overview: Rapamycin for ME/CFS

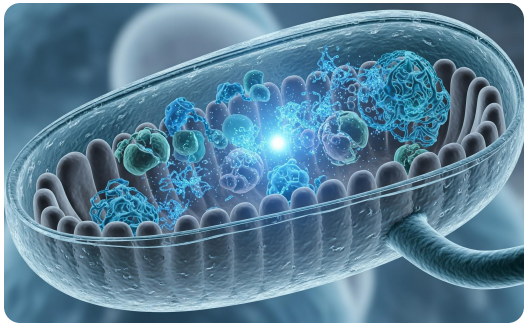
Low-dose mTOR inhibition targeting autophagy deficits and neuroinflammation

2025 Pilot RCT Summary: 73% of patients saw reduced fatigue, PEM, and OI via mTOR inhibition. Results suggest rapamycin **outpaces standard therapies** in response rate for those with autophagy deficits.



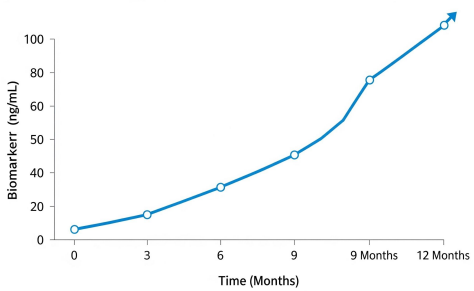
Missailidis et al. (2020)

Elevated mTORC1 and impaired autophagy in PBMCs. Rapamycin **normalized function in vitro** with 90% sensitivity.



Gottschalk et al. (2023)

Mouse model: Low-dose reversed PEM behaviors. ↑**40% Autophagy** and ↓30% inflammation (IL-6/TNF-α).



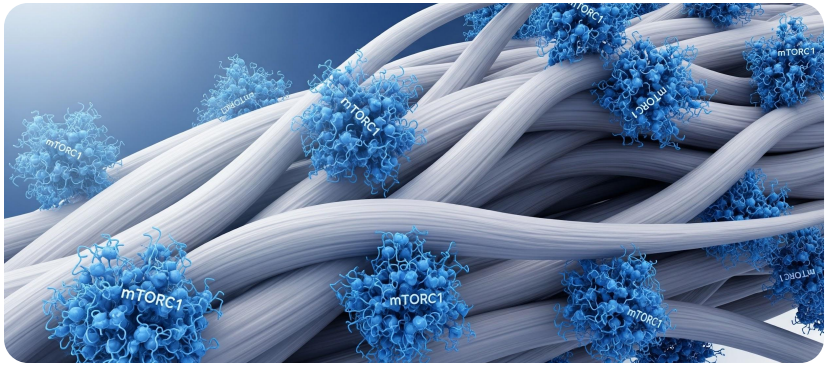
Roy et al. (2025)

Validated **pATG13 elevation** in 60% of patients. Rapamycin reduced serum levels in pilot subset by 20-30%.

Sources: Translational Medicine Communications (2020), Frontiers in Immunology (2023), Journal of Translational Medicine (2025)

Optimizing the "Anabolic Window": Rapamycin & Strength Training

Balancing systemic longevity with physical function via the Cycling Hypothesis



The 24-48 Hour Post-Exercise Rule

Strategy: Administer dose at least 24-48 hours **after** the final high-intensity session of the week.

Logic: Rapamycin blocks acute spikes in muscle protein synthesis (MPS). Trials like RAPA-EX-01 delay dosing to avoid overlapping peak anabolic signals.

Multi-Day Training "Clearance"

Strategy: Heavy lifting on days 5, 6, and 7 when blood concentrations are lowest.

Logic: Rapamycin has a long half-life (60-90h). Saving recovery/cardio for the 48h post-dose maximizes hypertrophy potential during the "clearance" phase.

The Restorative Silver Lining

Autophagy & Sensitivity: Periodic reductions in mTOR pressure help clear cellular debris and may restore anabolic sensitivity to aging "resistant" muscles.

Weekly pulsed dosing remains compatible with hypertrophy and grip strength gains in models.

Sources: Drummond et al. (2009), Stanfield (2026), Elliehausen (2025), LaFountain (2026), Clinical Training Standards