

SIROLIMUS: A PROMISING COMPOUND FOR LONGEVITY

What Is Sirolimus?

Sirolimus (commonly referred to as rapamycin) is a compound which was serendipitously discovered in naturally occurring soil sources on the island of Rapa Nui in 1972. Since its discovery, sirolimus has been used to regulate immune function, as an antifungal, and as an anti-inflammatory.¹ More recently, low doses of sirolimus are being used to increase lifespan and longevity by improving cellular detoxification, energy, and overall quality of life.

The FDA-approved uses for rapamycin (sirolimus) include the prophylaxis of organ rejection following renal transplant and the rare progressive lung disease lymphangioliomyomatosis (LAM). Additionally, rapamycin-eluting stents help prevent vessel re-narrowing of coronary arteries following surgery.

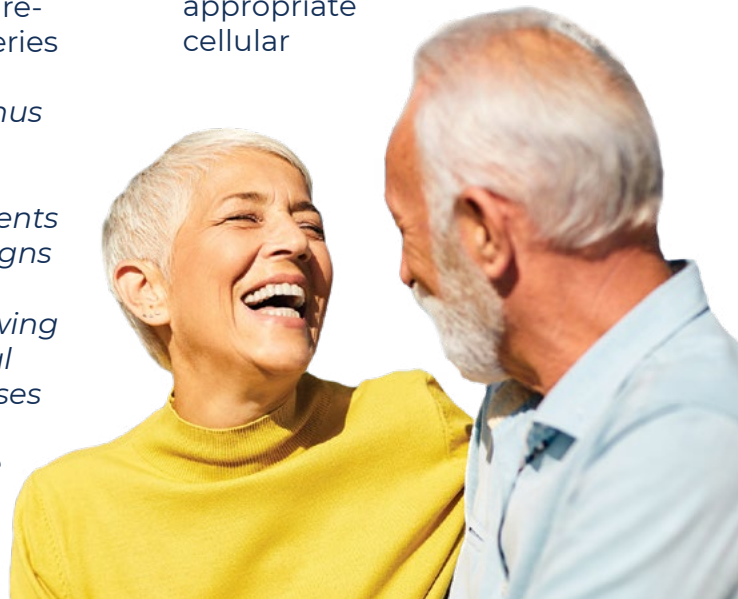
Important: *When sirolimus is dosed intermittently for longevity, versus daily for immunosuppression, patients do not exhibit the same signs of immunosuppression as they do when dosed following organ transplant. The goal with compounded low doses of sirolimus is to regulate, not suppress, the immune system. Below we will discuss further how the*

immunoregulatory properties of sirolimus dosed intermittently help to extend lifespan and healthspan.

How Does Sirolimus Work in the Body?


Sirolimus is an mTOR (mechanistic target of rapamycin) inhibitor which can help regulate the immune system and provide life-extending benefits. As indicated by the name, mTOR is the cellular target in the body where rapamycin binds, which was named following the discovery of the rapamycin compound. mTOR is important in regulating a wide range of functions in the body including cellular autophagy, proliferation, onset of age-related disease, and routine apoptosis.

When nutrients are available to the body (postprandial), mTOR turns on cellular metabolism, increasing anabolic processes and cellular growth and proliferation. When nutrients are scarce (fasting), mTOR is inhibited, so cellular autophagy, cellular repair, and regeneration can occur. Ideally, the mTOR pathway should be in balance between the growth and rest states, to maintain appropriate cellular



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turnover and repair. The mTOR signaling pathway is a fundamental regulator of cancer cells, chronic inflammatory conditions such as arthritis, metabolism, insulin sensitivity, and cellular autophagy. Regular periods of autophagy are critical for health and longevity.

What Is Sirolimus Used For?

Low doses of compounded sirolimus dosed intermittently (generally 5mg once per week) are used to increase health span by improving cellular autophagy, mimicking intermittent fasting, increasing energy, reducing inflammation and increasing lifespan. Sirolimus 7.5mg and 10mg compounded oral capsules are also available and typically follow a different dosing frequency such as once every 10 or 14 days.

Studies show that when mice were given rapamycin early in life, the treatment was sufficient to increase life expectancy up to 60%. And when given late in life, rapamycin may increase lifespan by 9–14%, which equates to roughly 7 years of extended human lifespan when treated with oral rapamycin (sirolimus).² The Participatory Evaluation of Aging with Rapamycin for Longevity (PEARL) Study is an active randomized, placebo-controlled trial further evaluating the safety and efficacy of rapamycin in

humans and is anticipated to be completed in December 2023.

COMMON BENEFITS REPORTED BY OUR PATIENTS TAKING COMPOUNDED SIROLIMUS INCLUDE:

- Improved energy
- Decreased brain fog
- Improved mood
- Decreased inflammation and chronic pain (especially in the joints and back)
- Smoother, tighter skin
- Weight maintenance/loss
- Healthier and faster-growing fingernails and toenails
- Improved bowel movement quantity and regularity

SIROLIMUS MAY ALSO IMPROVE THE FOLLOWING CONDITIONS:

- **Cancer:** Combats overexpression of mTOR associated with tumor growth
- **Cardiovascular:** Lowers inflammation, inhibits smooth muscle proliferation/vessel re-narrowing
- **Multiple Sclerosis:** Reduces mean brain plaque area size and disability status³
- **Rheumatoid Arthritis:** Provides a major reduction in disease activity score (swelling and tenderness), increases T regulatory cells, and may decrease the need for immunosuppressant use

- **Active Uveitis:** Decreases inflammation, helps reduce use of corticosteroids⁴
- **Weight Loss:** Communicates “excessive nutrient” signal to hypothalamus, mimics caloric restriction, decreases leptin synthesis and adiposity
- **Osteoporosis:** Reduces bone pain in metastases, promotes healthy new bone, regulates bone metabolism, activates autophagy in bone cells
- **Hearing Loss:** Delays progression and decreases acute symptoms
- **Periodontal Disease:** Delays onset and reduces gingival and periodontal bone inflammation
- **Glaucoma:** Improves dysregulated glucose metabolism which leads to optic nerve degeneration

How Is Sirolimus Dosed?

One 5mg oral capsule of sirolimus taken just once every 7 days is the generally recommended dose to achieve life extension and health span benefits. Most people can benefit from sirolimus because it inhibits the mTOR pathway. Those who require less help inhibiting the mTOR pathway may take a dose every 10 or 14 days. Doses of sirolimus 7.5mg may be recommended every 10 days, and sirolimus 10mg may be dosed every 14 days. Dosing of sirolimus is based on patient response,

considering improvement and any side effects.

Dosage adjustments are not necessary for those with altered kidney function. However, for those with altered hepatic function, decreasing the frequency of dosing is advised (once weekly to twice monthly).

How Long Does It Take for Sirolimus to Work?

Patients should experience a noticeable increase in energy and decrease in inflammation roughly 2–3 days following their first dose. If they do not experience any noticeable benefit after 3 months of consistently taking sirolimus, it may not be beneficial for them, and their mTOR pathways may already be functioning optimally, so consider discontinuing sirolimus.

What Are the Side Effects and Safety Profile of Sirolimus?

When dosed intermittently and for life-extending purposes, sirolimus should not elicit any side effects suggestive of immunosuppression. The goal of treating with low doses of sirolimus is to improve mTOR inhibition, energy, and cellular autophagy.

One potential side effect to monitor is aphthous ulcers on

the inside of the mouth, which may indicate some weakening of immunity. If ulcers occur, decrease the frequency of dosing and the ulcers should quickly resolve (adjust once every 7 days to once every 10 days). Rinsing the mouth with saltwater is also helpful. In our patients, the incidence of these ulcers occurring has been far less than 1%.

Since sirolimus is considered a life-extending compound, and the ability to inhibit mTOR seems to decline with age, it does not make much sense for individuals who are still growing or under the age of 25 years to use sirolimus for these purposes. In general, those over 25 years of age can benefit greatly from sirolimus. However, for younger patients (< 25 years old) suffering from more serious chronic conditions, such as Ehlers-Danlos syndrome (EDS), for example, the benefits of sirolimus treatment have been shown to greatly outweigh the risks.

Tracking Progress of Patients Taking Sirolimus

For your benefit and the benefit of your patients, utilizing a Medical Symptoms Questionnaire (MSQ) is helpful to evaluate their month over month improvement on

compounded sirolimus. The MSQ total score should decrease each month for patients taking sirolimus, indicating symptom improvement. Here is a link to the MSQ we recommend incorporating into your patient materials:

<https://tinyurl.com/yp8fwwwn>

It is unlikely that sirolimus will excessively inhibit the mTOR pathway, but it can still be beneficial to monitor parameters impacting the patients' immune response, such as blood sugar, RBCs, WBCs, serum triglycerides, and iron status.

As described, mTOR inhibition and routine cellular autophagy are essential for increasing the health span and life expectancy of our patients. Compounded sirolimus, when dosed intermittently at low doses, supports crucial cellular autophagy, also allowing the body to respond maximally to adjunct treatments and therapies. We have been beyond pleased with our patients' response to sirolimus, and we would be happy to discuss its benefits with you.

REFERENCES

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