Clinical Evaluation of mTORC1 Inhibition for Geroprotection
“Everolimus Aging Study (EVERLAST)"


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Abstract

The number of older individuals is expected to reach 2 billion by the year 2050 and age is one of the greatest risk factors for nearly every chronic disease. Inhibition of mTORC1 signaling with the drug rapamycin extends lifespan of model organisms and prevents or delays age-related changes in multiple organ systems. However, the risk of adverse side effects in humans has prevented the use of the mTOR inhibitor rapamycin or rapamycin analogs (rapalogs) as a therapy for aging and age-related diseases.

Therefore, it remains unknown if mTOR inhibitor-based therapies can extend healthy lifespan in humans. Our team has demonstrated that while inhibition of mTORC1 is beneficial and extends healthy aging in mice, many of the negative side effects of rapamycin result from "off-target" inhibition of a second mTOR complex (mTORC2) in multiple tissues. We and others have identified that low daily or intermittent dosing schedules of rapamycin and rapalogs enable more selective mTORC1 inhibition and minimize adverse effects. The purpose of this project is to determine if 24 week intermittent dosing of daily low dose or weekly intermittent dosing (5 mg/week) with the mTORC1 inhibitor everolimus can safely improve physiological and molecular hallmarks of aging in middle-aged to older insulin resistant (IR) adults (n=24/group, 55-80 yrs old). We will study IR adults for several important reasons. IR adults 1) are free of overt disease, which permits the study of aging and not end-stage disease, 2) represent most of the U.S. aging population, 3) are characterized by hyperactive mTORC1 activity, and 4) have increased risk for nearly every age-related chronic condition, including type 2 diabetes (T2D), cardiovascular disease (CVD), frailty, dementia and immunosenescence. Importantly, these are all age-related conditions that have been delayed or prevented by mTORC1 inhibition in model systems. Therefore, IR subjects are the ideal candidate population to test if mTORC1 inhibition by everolimus can improve physiological function to delay or prevent the onset of age-related chronic conditions. Using a randomized, placebo-controlled clinical trial, we will perform a battery of gold-standard and innovative techniques to test the hypothesis that daily low dose or weekly everolimus treatment will improve 5 inter-related domains of physiological aging: metabolic, cardiac, cognitive, physical, and immune function. We will also assess the incidence of adverse events and changes from baseline blood chemistry, hematology, lipids, glucose, and insulin. To comprehensively examine the molecular target specificity and the impact on mechanisms of aging by everolimus, we will evaluate mTORC1 and mTORC2 signaling, assess mitochondrial bioenergetics, and perform a multi-omics approach (epigenomics, transcriptomics, lipidsomics, and metabolomics) in blood and muscle biopsy samples. By completion of this study, we expect to understand whether inhibition of mTORC1 can have geroprotective effects in humans at risk for multiple age-related chronic conditions.

Study Rationale

mTORC1 inhibition increases lifespan in older, insulin resistant animals

Current mTORC1 based therapeutics in humans have safety concerns

Negative side effects of rapamycin in mice result from "off-target" inhibition of mTORC2

Selective inhibition of mTORC1 with the rapalog everolimus inhibits mTORC1 but not mTORC2

Study Design

Background

10 Common Chronic Conditions for Adults 65+

Rapamycin is a drug discovered from the soil of Easter Island.

mTORC1 regulates growth, metabolism and aging. Its activation has been implicated in metabolic dysfunction, cancer and CVD. Rapamycin acutely inhibits mTORC1, but chronically inhibits mTORC2.

Inclusion Criteria

• Young (18-35 years old) or older adults (55-80 years old)
• IR (HOMA >1.5)
• Prediabetic fasting glucose 100-125 mg/dL, HbA1c of 5.7-6.4%)
• Not planning to change diet or physical activity during study

Outcomes

Pre-Intervention Physiological Tests:
-DEXA
-VO2 Max
-IR Function
-ECO
-HbA1c
-Total cholesterol
-Triglycerides
-Cardiac Function
-Insulin sensitivity
-Immunocompetence

everolimus
-Weekly placebo

Placebo

Placebo

Placebo

Post-Intervention Physiological Tests:
-DEXA
-VO2 Max
-Muscle Function
-ECO
-Cardiac Function
-Insulin sensitivity
-Immunocompetence

Placebo

Placebo

Placebo

Study Innovation

• First study to test whether or not a rapalog can improve physiological function across multiple aging domains such as metabolic, cognitive, cardiac and immune function.
• Study population involves IR people who are at high risk for age-related diseases
• Co-investigator Dr. Lamming has shown that mice treated with intermittent rapalogs reduce off-target metabolic and immunosuppressive effects of mTORC2 inhibition – we want to see if these findings can be replicated in humans
• Investigate if DNA methylation can revert towards that of young, healthy controls
• Explore if mTORC1 inhibition can decelerate epigenetic aging as assessed by the four epigenetic clocks: Horvath, Hannum, PhenoAge and GrimAge

Outcomes

• Change in heart function – look at blood flow to certain regions of the brain (hippocampus).
• Change in cognitive function – assess response to seasonal flu vaccination through HI titer.
• Change in immune function – assess response to seasonal flu vaccination through HI titer.
• Change in metabolism of mTORC1 and mTORC2 downstream targets (inhibit mTORC1 but not mTORC2).

Acknowledgements

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