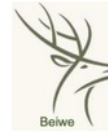


# Beiwe: Novel mTORC1 inhibitors to extend Healthspan and Longevity



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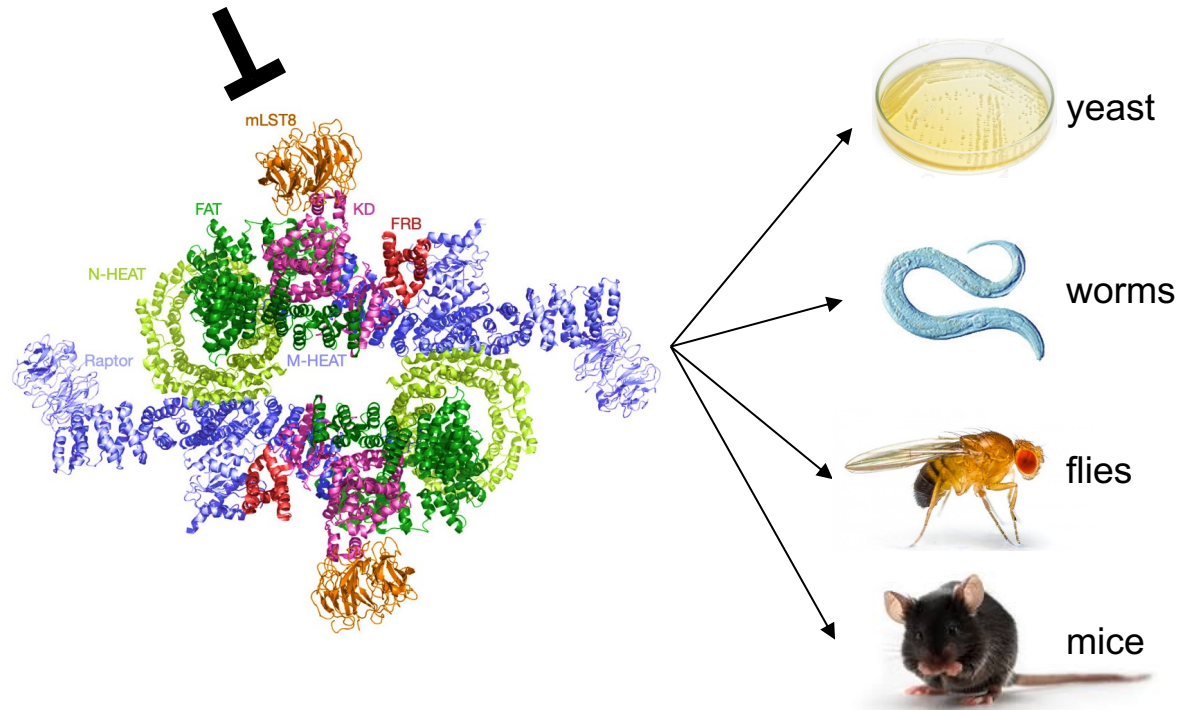




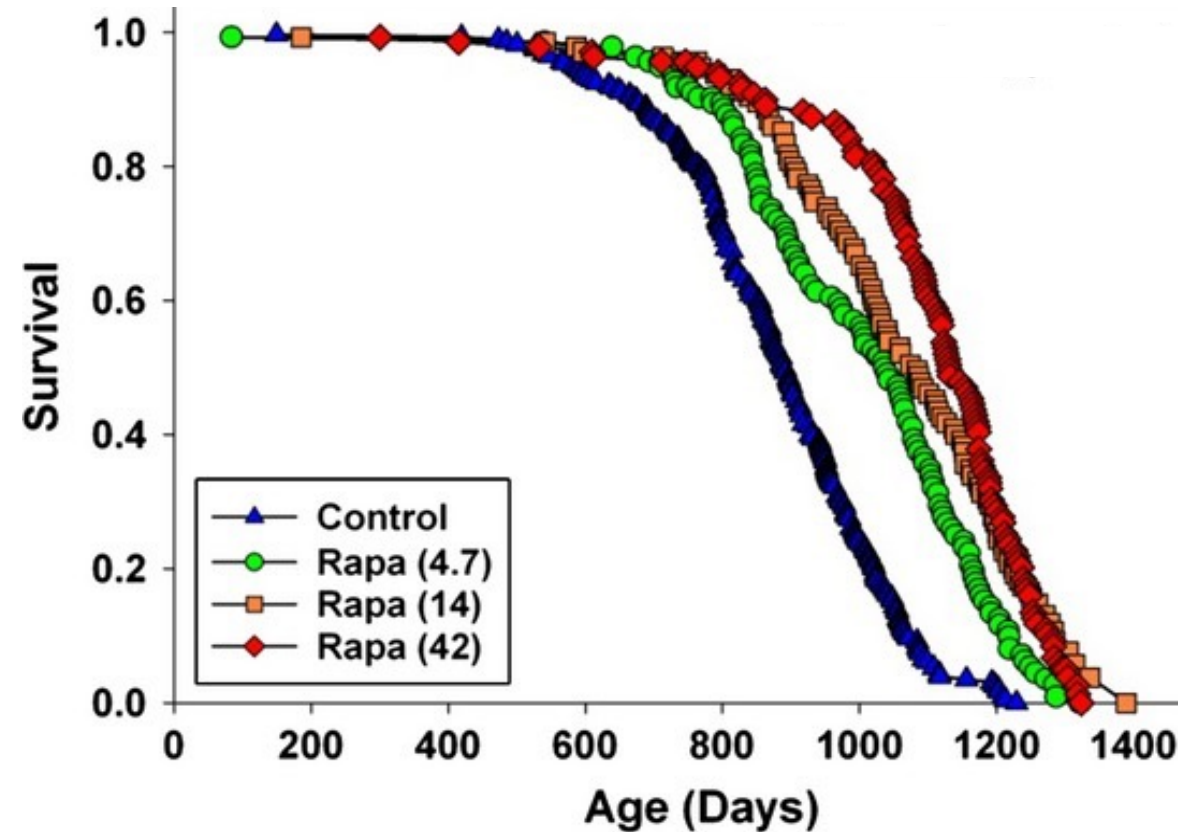
# mTORC1 is the most validated drug target for **longevity** across multiple species

mTORC1 inhibition by Rapamycin

Extends Lifespan in:



Mouse Lifespan Extension is dose-dependent with mTORC1 inhibitor



Miller R. A. Aging Cell. 2014 Jun; 13(3): 468–477.

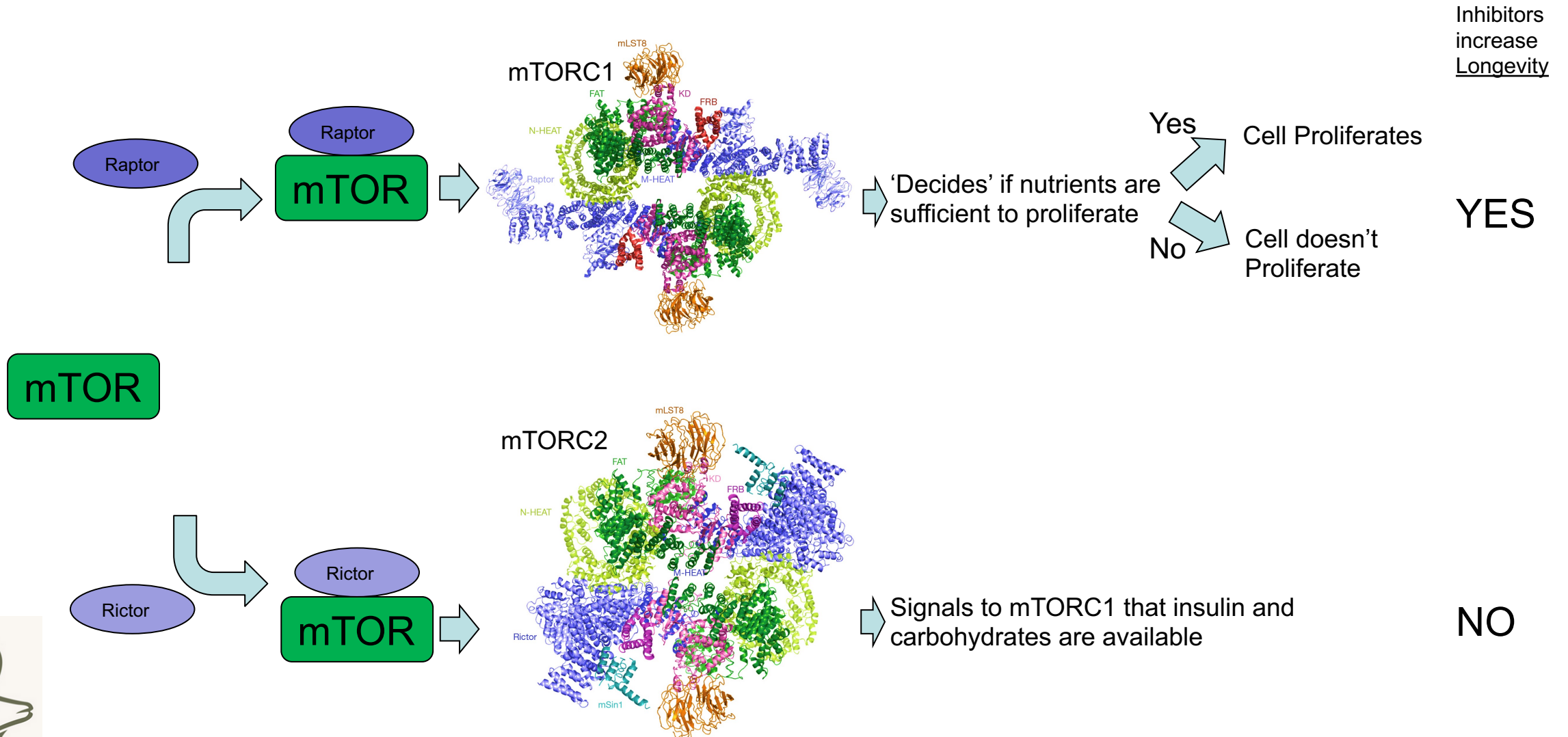




mTOR exists in two forms mTORC1 and mTORC2 in the cell:

mTORC1 → Overall integrative sensor of Nutrient Availability, it Regulates Cell Proliferation, and Longevity

mTORC2 → A sensor of Insulin Availability, doesn't regulate longevity, its inhibition produces side effects



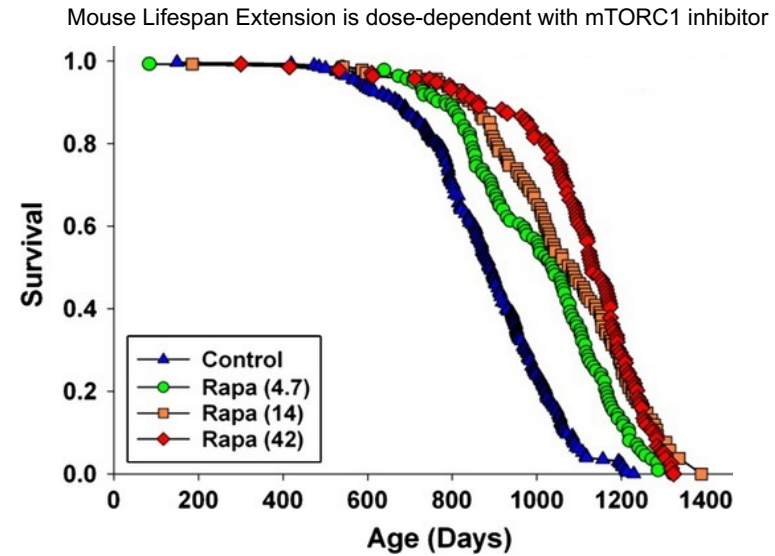
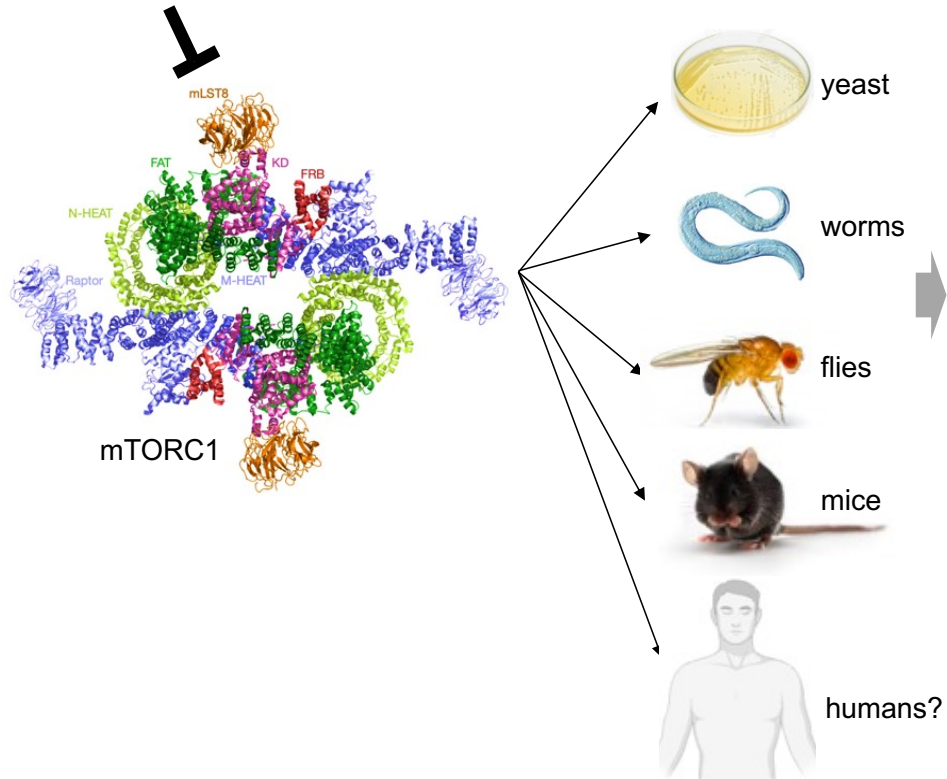


# So why not simply use Rapamycin to Extend Human Lifespan?

(it should work, right?)

mTORC1 inhibition by Rapamycin

Extends Lifespan in:



Miller R. A. Aging Cell. 2014 Jun; 13(3): 468–477.





Two reasons Rapamycin won't likely be developed as a longevity medicine:

1 : Clinical trial in healthy older adults: Rapamycin produces *substantial side effects*

Rapamycin Side Effect Profile→

~40% dropout rate in elderly humans, associated with:  
*Gastrointestinal issues*  
*Rash*  
*Anemia: Red Blood Cell and Hematocrit deficits*

Experimental Gerontology. 2018 May;105:53-69. doi: 10.1016/j.exger.2017.12.026..

A randomized control trial to establish the feasibility and safety of rapamycin treatment in an older human cohort: Immunological, physical performance, and cognitive effects

Ellen Kraig<sup>a,b,\*</sup>, Leslie A. Linehan<sup>b</sup>, Hanyu Liang<sup>a</sup>, Terry Q. Romo<sup>a,g</sup>, Qianqian Liu<sup>c</sup>, Yubo Wu<sup>e</sup>, Adriana D. Benavides<sup>d</sup>, Tyler J. Curiel<sup>a,e</sup>, Martin A. Javors<sup>a,f</sup>, Nicolas Musi<sup>a,e,g</sup>, Laura Chiodo<sup>g</sup>, Wouter Koek<sup>b,f</sup>, Jonathan A.L. Gelfond<sup>a,c</sup>, Dean L. Kellogg Jr.<sup>a,e,g</sup>

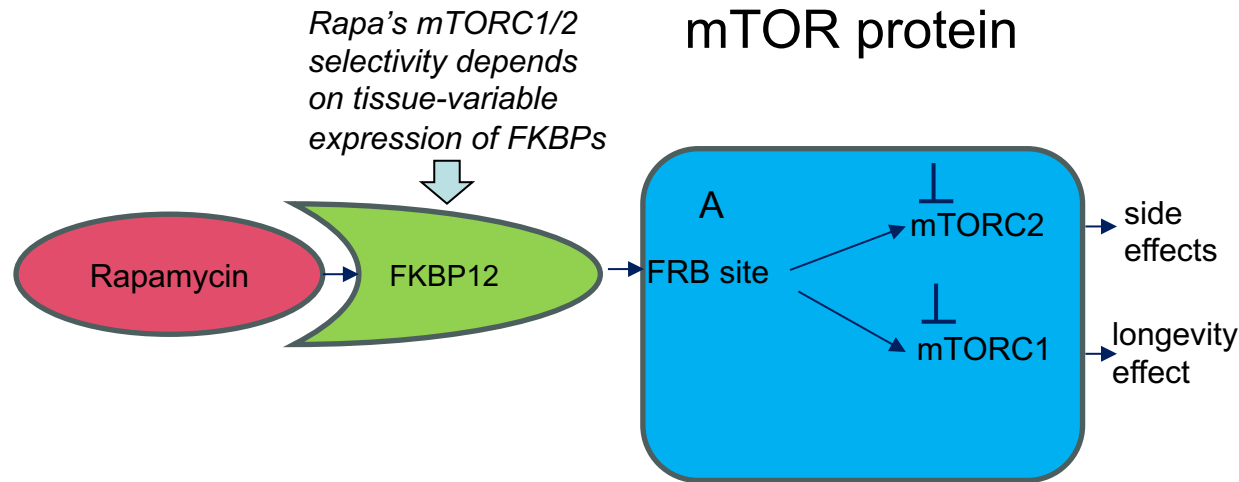
<sup>a</sup>Barshop Institute for Longevity and Aging Studies, The University of Texas Health Science Center, San Antonio, USA

2 : Rapamycin and most rapalogs patents are expired or limited, making it more difficult for pharma or VC to invest→no Return on Investment



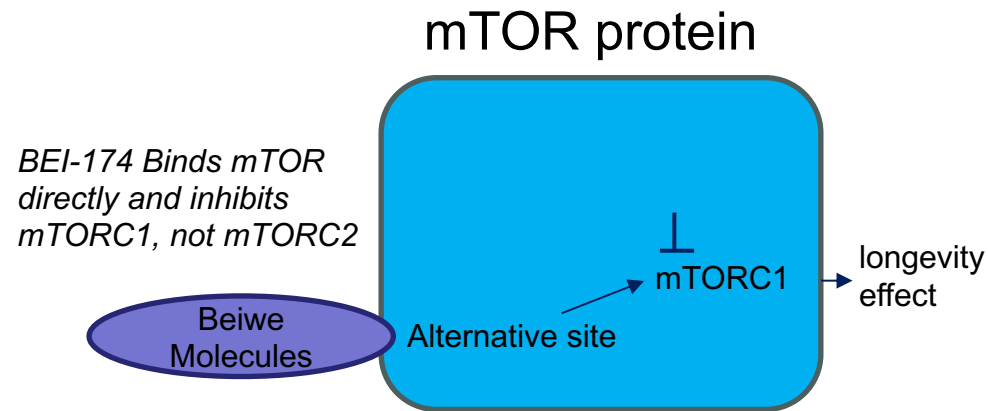


Why does Rapamycin produce side effects? Because in addition to mTORC1 (longevity) it also inhibits mTORC2



Rapamycin inhibits both mTORC1 AND mTORC2, producing longevity AND side effects

By contrast Beiwe's molecules engage mTOR directly, and their mechanism is completely mTORC1 specific

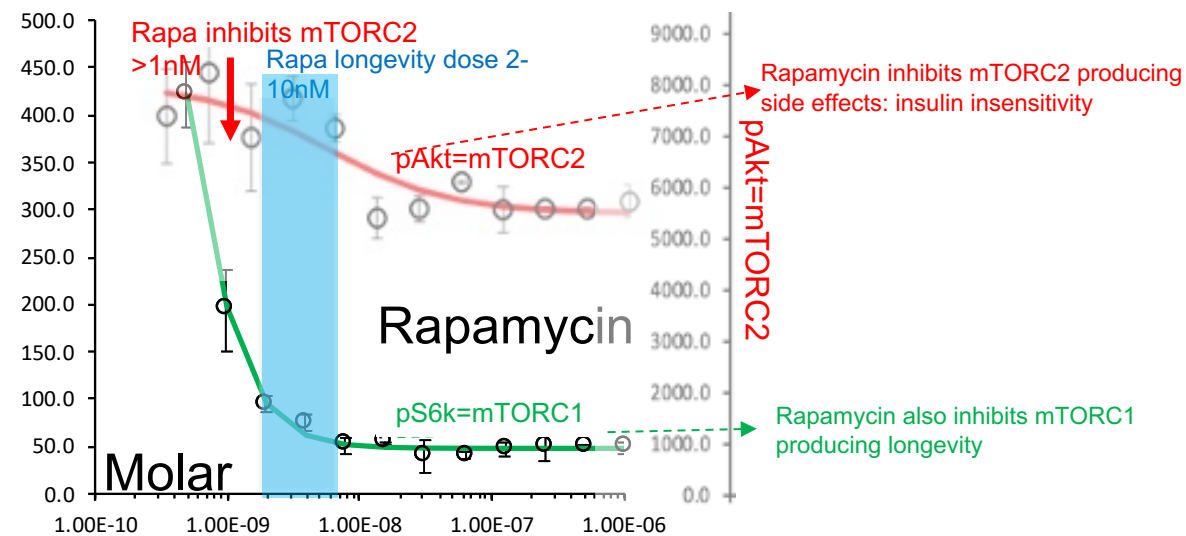
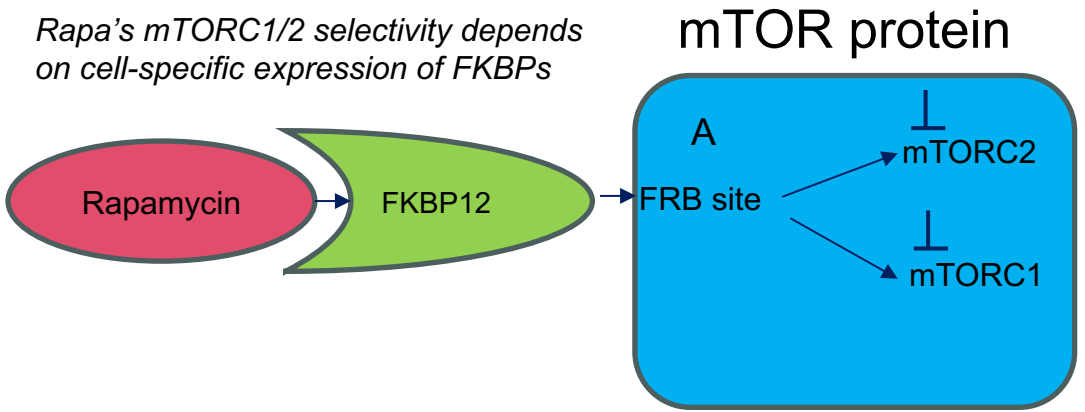


Beiwe's molecules engage mTOR at a different site, that ONLY inhibits mTORC1, producing the longevity effect with less side effects

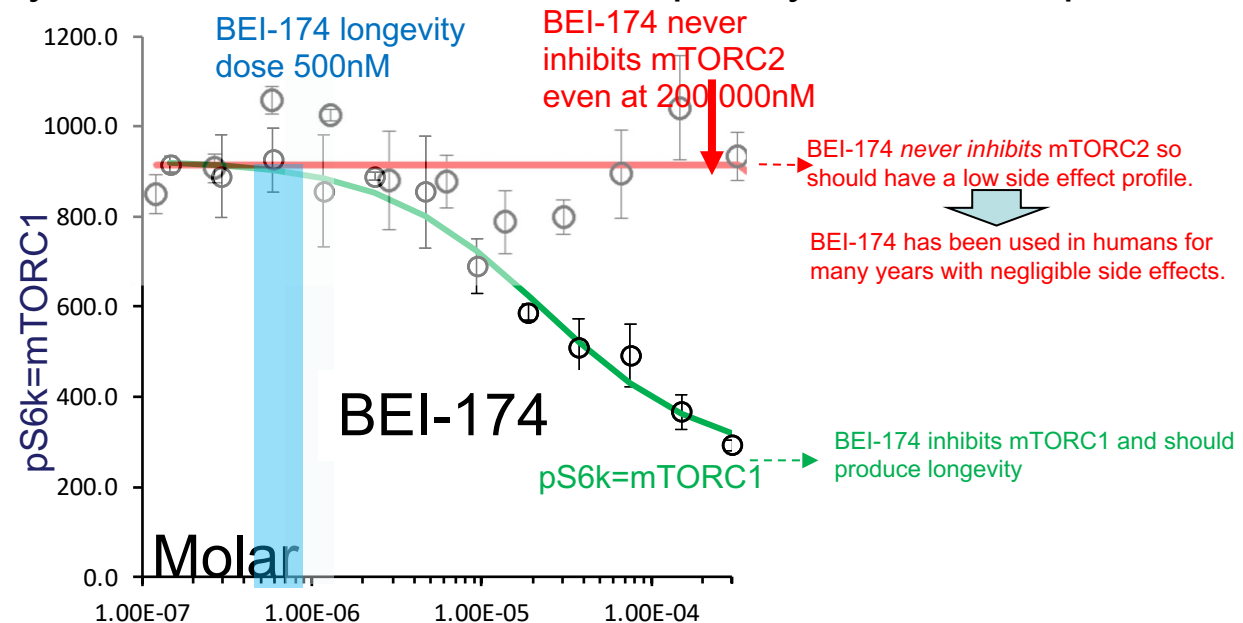
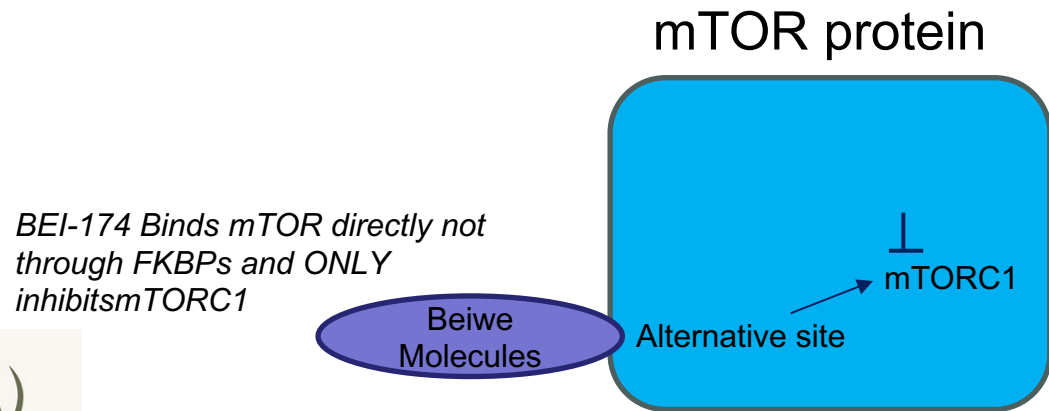




Can one avoid Rapamycin side effects by using a lower dose?  
 No, because the Rapamycin dose that causes longevity also causes mTORC2 inhibition & thus side effects

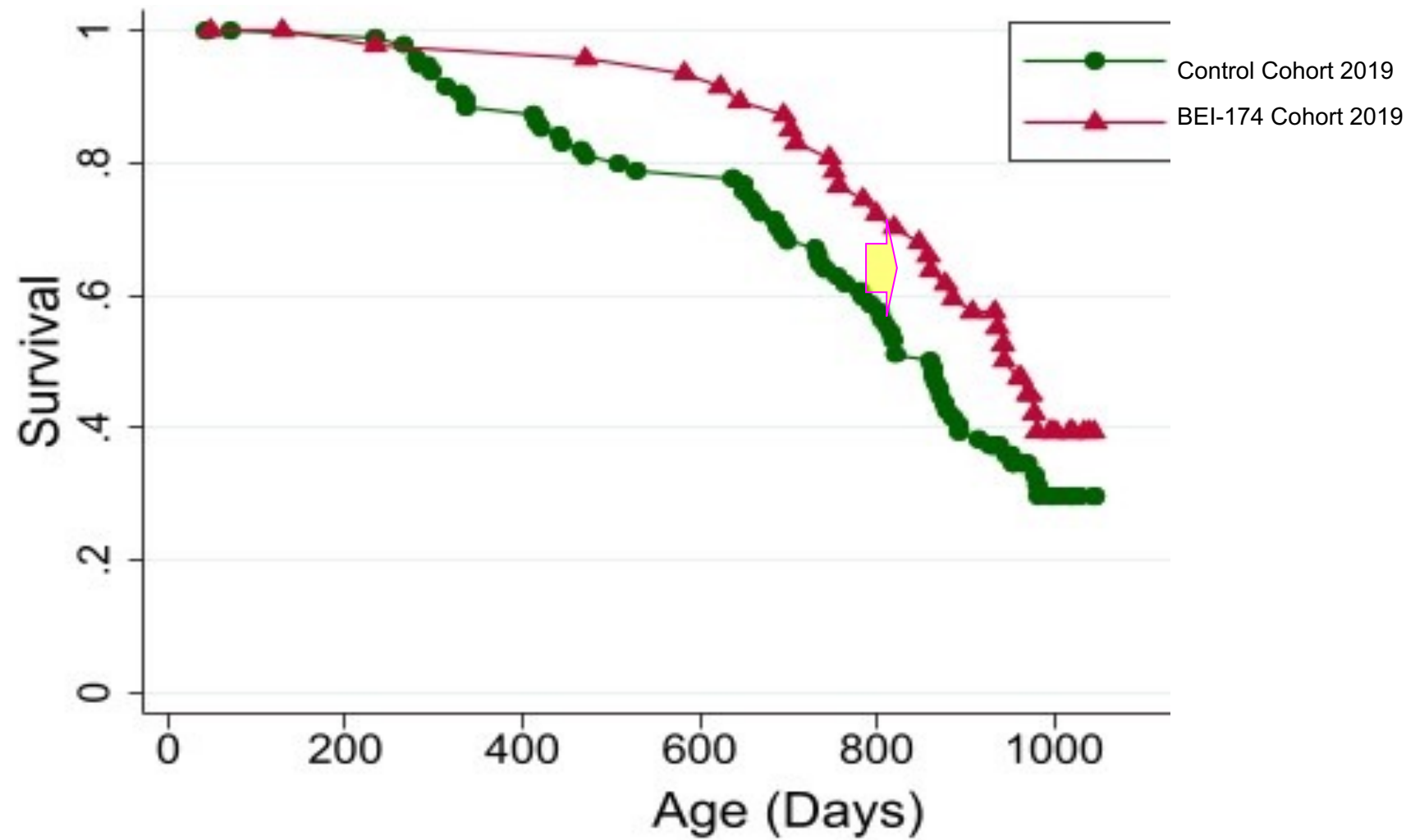


By contrast Beiwe's molecules engage mTOR directly, and their mechanism is completely mTORC1 specific





NIH's Interventions Testing Program: BE1-174 Significantly extends lifespan in mice.

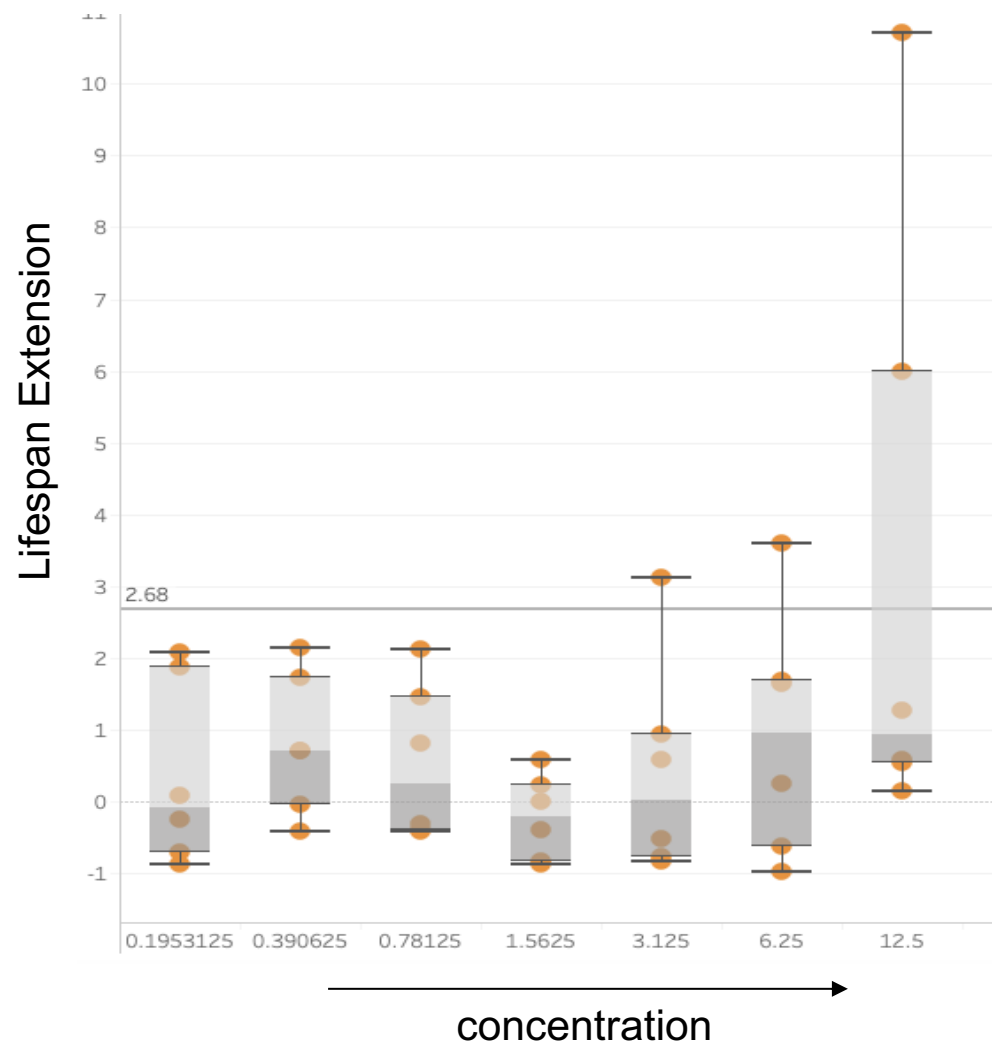


Astaxanthin and meclizine extend lifespan in UM-HET3 male mice:...Harrison DE...Cortopassi G... Miller RA. Geroscience. 2023 Dec 2. doi: 10.1007/s11357-023-01011-0. Online ahead of print. PMID: 38041783



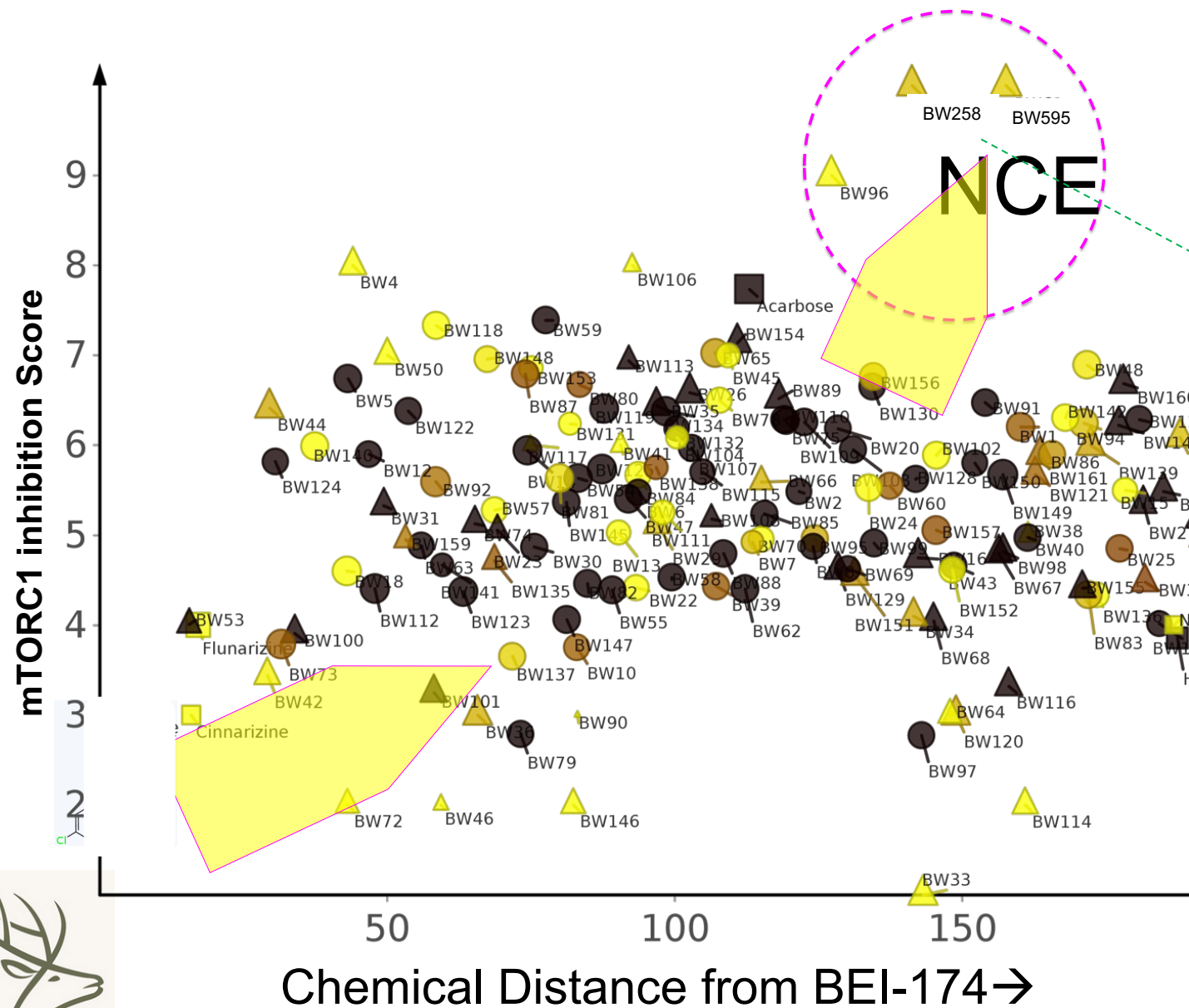


# BEI-174 Dose-dependently extends lifespan in yeast

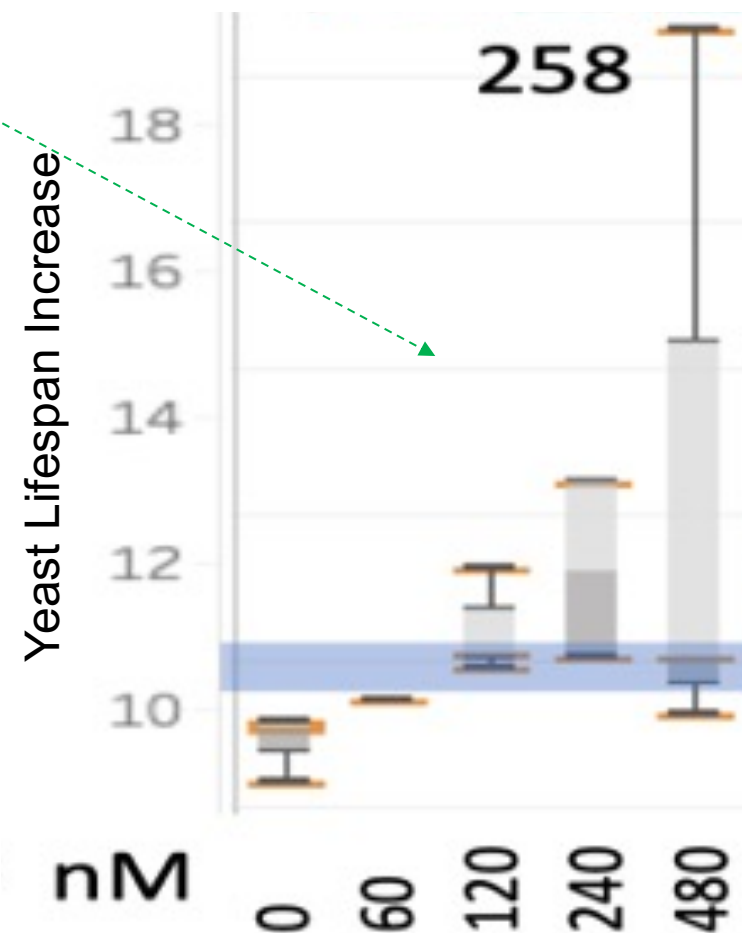




Beiwe used Medicinal Chemistry to identify novel scaffolds more potent for mTORC1 inhibition



BEI-258 dose-dependently:  
binds mTOR  
inhibits mTORC1  
extends yeast lifespan





## Beiwe's Molecules

1. Engage mTOR at a novel site that *only* causes inhibition of mTORC1, not mTORC2.
2. Repurposed molecules that engage this novel site are safe in humans and brain-penetrant.
3. BEI-174 significantly extends lifespan of mice and yeast.
4. We have designed and synthesized novel scaffolds and New Chemical Entities (BEI-258, 595) that engage this site.
5. These NCEs are more potent and dose-dependently extend yeast lifespan.
6. Beiwe seeks investment to identify clinical lead candidates to extend Healthspan and Longevity.





## Beiwe's Unique Therapeutic Proposition

Beiwe is named after the Finnish goddess of health. Beiwe is developing medicines that extend longevity and kill cancer cells.



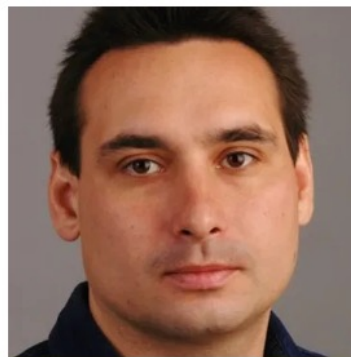
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