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"Chemistry of Longevity:
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Rapamycin:
An intriguing natural product

July 18, 2016
Exotic origins

James A. Boutillier and Stanley C. Skoryna

27-minute video on the expedition:
https://youtu.be/ikrQubXJuOo

Suren Sehgal
(also known as Rapamune and sirolimus)

http://www.sehgal.net/surenshistory.htm
Rapalogs and mTOR

Developed at Wyeth (now Pfizer)

Developed at Novartis

Science, 1996, 273, pp. 239-242

New York Times
May 16, 2016

Dogs Test Drug Aimed at Humans’ Biggest Killer: Age

C&en

New York Times
May 16, 2016
The Chemistry of Longevity: Rapamycin

Matt Kaeberlein
Department of Pathology
University of Washington

Major causes of disability and death

What are the biggest risk factors?

- Alzheimer’s Disease
- Cognitive Decline
- Immune Decline
- Type II Diabetes
- Cancer
- Kidney Disease
- Cardiovascular Disease
- Arthritis & Osteoporosis
Aging is the greatest risk factor for disease

How much do you think life expectancy would be increased for a typical 50 year old woman if we could cure all forms of cancer today?

- Greater than 20 years
- 10 - 15 years
- 3 - 5 years
- No change
What if aging could be slowed?

<table>
<thead>
<tr>
<th>Increase in life expectancy for a 50 year old woman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure cancer</td>
</tr>
<tr>
<td>~ 3-5 years</td>
</tr>
<tr>
<td>Still with chronic disease and disability</td>
</tr>
<tr>
<td>Cure cancer, heart disease, stroke, and kidney-related disease</td>
</tr>
<tr>
<td>~8-10 years</td>
</tr>
<tr>
<td>Still with chronic disease and disability</td>
</tr>
<tr>
<td>Slow aging 50%</td>
</tr>
<tr>
<td>~15-25 years</td>
</tr>
<tr>
<td>These extra years are spent in relatively good health!!!</td>
</tr>
</tbody>
</table>

“The Longevity Dividend”

Martin et al. Science 299, 1339-1341, 2003

Rapamycin: the first effective longevity drug?
Rapamycin: It all started on Rapa Nui

- Identified in 1972 in soil samples from Easter Island
- Isolated from *Streptomyces hygroscopicus*
- Antifungal, anti-proliferative properties
- FDA approved for organ transplant in 1999
- Sirolimus = rapamycin; everolimus, temsirolimus, deforolimus/ridaforolimus are ‘rapalogs’

TOR gene first isolated in budding yeast

- Rapamycin resistant mutants identified in FPR1 (FK506 binding protein), TOR1, TOR2
- Yeast TOR1, TOR2 homologous to mammalian mTOR
- mTOR: TOR = ‘target of rapamycin’; m = “mammalian” or “mechanistic”
- Two TOR complexes:
  - TORC1 (TOR1/TOR2)
  - TORC2 (TOR2)
Diverse function of two mTOR complexes

- Rapamycin does not directly inhibit mTORC2
- “Chronic” rapamycin treatment can influence mTORC2

Inhibition of mTORC1 increases life span

Regulation of Yeast Replicative Life Span by TOR and Sch9 in Response to Nutrients

The TOR pathway interacts with the insulin signaling pathway to regulate C. elegans larval development, metabolism and life span
Jia et al., Development 131: 3697-3604.

Influence of TOR kinase on lifespan in C. elegans

Regulation of Lifespan in Drosophila by Modulation of Genes in the TOR Signaling Pathway
Kapahi et al., Curr Biol 14: 885-890.
Rapamycin increases life span


Robida-Stubbs et al., Cell Metab 15: 721-734.

Bjedov et al., Cell Metab 11: 35-46.

Rapamycin: longevity and healthspan in mice

- First shown to increase lifespan in middle-aged mice
  - Starting treatment at 20 months = 10-15% increase
- Improves healthspan in mice: cognitive, muscle, cardiac, immune, kidney, stem cells, …
- Improves age-related disease models in mice: cancers, Alzheimer’s disease, obesity, muscular dystrophy, dilated cardiomyopathy, mitochondrial disease…

For review see Johnson et al., Interdiscip Top Gerontol. 40:107-27. 2015
How is rapamycin affecting lifespan?

Hallmarks of Aging

- Genomic instability
- Telomere shortening
- Epigenetic changes
- Loss of proteostasis
- Deregulated nutrient signaling
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Altered cell-cell communication

Mid-life almost as good as life-long treatment

- Tested in mice by NIA Interventions Testing Program
- Encapsulated in food (2.2 mg/kg/day; 14 ppm = 1X ITP)
- First study began treatment at 600 days of age; second study began treatment at 9 months
- Since replicated in >10 studies, 3 strain backgrounds

![Graphs showing survival curves](image1)

Lifespan effects are sex-, dose-dependent

- Treatment initiated at 9 months
- Female effect > males for lifespan
- Encapsulated in food: 4.7 ppm < 14 ppm < 42 ppm for lifespan

![Graphs showing survival curves](image2)
Short-term rapamycin has benefits for health

- 6-10 weeks of rapamycin improves cardiac and immune function in old mice
- Evidence for similar immune effects in people

12 weeks of rapamycin extends mouse lifespan

- Two doses tested;
  - Bigger effects in males
  - Highest dose did not extend females
- Shift in cancer spectrum in females
- Improved muscle function
- Remodeling of the microbiome
Which of these is the most effective at extending lifespan and health span in mice?

A. Metformin  

B. Acarbose  

C. Resveratrol  

D. Rapamycin  
So why aren’t we all taking rapamycin?

- Some potential side effects of rapamycin
  - Cataracts (mouse)
  - Decreased spermatogenesis (mouse)
  - Insulin resistance (mouse*, human)
    *Glucose tolerance test; no diabetes
  - High triglycerides (human)
  - Diarrhea and nausea (human)
  - Mouth ulcers (human)
  - Thrombocytopenia (low blood platelets, human)
  - Risk of infection (human)
  - Impaired wound healing (mouse, human)

- Given at high doses to sick patients taking other meds
- Lower doses or transient treatments will reduce side effects – will they be effective at improving healthspan or lifespan?

How do we get from mice to people?

- Problem: How do we get from interventions in mice to healthy aging in people?
  - Unregulated supplements (mostly scams)
  - Clinical trials –
    - Interventions that target aging may not work in people who are already sick
    - Currently not possible to directly test aging
How do we get from mice to people?

Our approach: Companion (pet) dogs represent an optimal intermediate step

www.dogagingproject.com

Why this makes so much sense

• Age similarly to humans – but much more rapidly
  • Can know the answer in 3-5 years
• Genetic and phenotypic diversity
• Share our environment
• Engages the public in ‘citizen science’
• Will convince people this is possible in humans
• Improve the quality of life for pets and owners
Longitudinal study of aging in dogs

- Goal is to understand the genetic and environmental factors that influence healthy aging in dogs
- Hope to enroll 10,000+ dogs

Rapamycin trial in companion dogs

- Goal to determine whether rapamycin can increase lifespan and healthspan in pet dogs
- Start **low dose** rapamycin at 6-9 years
- Follow healthspan parameters and survival in treated and untreated animals for 3-5 years
Phase 1: Completed earlier this year

- 10 week treatment to establish dosing and effects on cardiac function
- 3 groups: placebo, lower dose, higher dose
- Entrance criteria:
  - At least 6 years old, at least 40 lbs.
  - No significant pre-existing conditions

Phase 1: 10 week study

- 40 dogs enrolled, 24 completed
  - 11 excluded (significant pre-existing conditions)
  - 4 lost to follow up (owner failed to complete study)
  - 1 removed from study
  - 24 completed study (8 placebo, 6 low rapa, 10 high rapa)
- No significant side effects
- Blood chemistry measures remained within normal ranges

Rapamycin Cardiac Data in Mice

- 10 weeks of rapamycin treatment in aged mice improves ejection fraction and fractional shortening (Flynn et al., Aging Cell 12:851. 2013)
  - EF% measures fraction of blood pumped out of the left ventricle each contraction
  - FS% is the ratio of left ventricle diameter when relaxed versus contracted;
- Improves E/A ratio (Dai et al., Aging Cell 13:529. 2013)
  - E/A ratio measures the function of the left ventricle; ratio of early (E) to late (A) filling

Comparison of Mice and Dogs

Mouse EF and FS from Flynn et al., Aging Cell 12:851. 2013
Mouse E/A from Dai et al., Aging Cell 13:529. 2013
Dog data, Dog Aging Project, unpublished
Phase 2: Starting later this year

- 50 mid- to large-size dogs, at least 6 years old
- One year treatment period
- Evaluation of:
  - Side effects
  - Blood chemistry
  - Cardiac function
  - Cognitive function

Phase 3: Hopefully mid-2017

- Mid- to large-size dogs, at least 6 years old
- National/International 5 year study
- 600 dogs treated with rapamycin or placebo and followed for health during aging
- Evaluation of:
  - Survival
  - Cardiac function
  - Cognitive function
  - Cancer incidence
  - Physical activity
  - Immune function
How do you feel about the possibility of taking low-dose rapamycin to increase your health span?

- Sign me up! I’m convinced.
- Not for me yet, but I’d give it to my dog
- I’ll wait a few years and see how the research progresses
- No way. Too risky for me. I’ll take my chances with old age
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