Theory Paper

Disease or not, aging is easily treatable

Mikhail V. Blagosklonny[1]

[1]Cell Stress Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA

Correspondence to: Mikhail V. Blagosklonny; **email:** mikhail.blagosklonny@roswellpark.org
Keywords: gerossuppresants, senolytics, longevity, lifespan
Received: August 15, 2018 **Accepted:** November 2, 2018 **Published:** November 17, 2018

ABSTRACT

Is aging a disease? It does not matter because aging is already treated using a combination of several clinically-available drugs, including rapamycin. Whether aging is a disease depends on arbitrary definitions of both disease and aging. For treatment purposes, aging is a deadly disease (or more generally, pre-disease), despite being a normal continuation of normal organismal growth. It must and, importantly, can be successfully treated, thereby delaying classic age-related diseases such as cancer, cardiovascular and metabolic diseases, and neurodegeneration.

Endless debate on aging and disease

For decades, one of the most debated questions in gerontology was whether aging is a disease or the norm. At present, excellent reasoning suggests aging should be defined as a disease [1-7]. I tend to define aging a disease, even though it is the norm. Vladimir Dilman referred to aging as "normal disease" [8, 9].

As I emphasized in my publications, aging is not programmed. I have explicitly stated as such even in my article titled "Aging is not programmed: genetic pseudo-program a shadow of development growth" (PMID: 24240128). Aging is a normal continuation of the normal develop-mental program, so it is NOT a program but a purposeless, unintended quasi-program [10-16]. Yet, aging is also a deadly disease because it inevitably leads to death.

Indeed, aging is "the sum of all age-related diseases" and this "sum is the best biomarker of aging" [17]. Aging and its diseases are inseparable, as these diseases are manifestations of aging. Of course, any one age-related disease can occur at a young age due to genetic and environmental factors. What is important is that aging is sufficient to cause all age-related diseases, sooner or later, without dependence on genetic or environmental factors [18]: if Alzheimer's disease or type 2 diabetes is not diagnosed during ones life time, it is only because cancer or a stroke terminates life before

Alzheimer's diseases or type 2 diabetes can be diagnosed (and vice versa).

Aging is the sum of pre-diseases and diseases

Aging is an increase in the probability of death due to age-related diseases, which are late manifestations of aging [18]. Diseases are preceded by pre-diseases. For example, diabetes is diagnosed when fasting glucose levels are higher than 125 mg/dl, while levels of 100 to 125 mg/dl are considered pre-diabetes. Remarkably, diabetic complications such as nephropathy and retinopathy often develop before type 2 diabetes itself (see for references [19]). Although not formally a disease, pre-diabetes is currently treated to prevent diabetes [20-23]. Moreover, pre-diabetes is initiated by underlying processes that we will call pre-pre-diabetes, which arise while fasting glucose levels and glucose tolerance are still normal, though insulin levels are increased (hyperinsulinemia), indicating mild insulin resistance [24]. Hyperinsulinemia in healthy adults with normal glucose levels is predictive of type 2 diabetes

over a 24-year follow-up [25, 26]. Normal glucose levels (<100 mg/dl) associated with hyperinsulinemia is pre-pre-diabetes [27]. Hyperinsulinemia may in turn be driven by mTOR signaling [19], which suggests a state of pre-pre-pre-diabetes in which both glucose and insulin levels are normal. The condition that we can call pre-pre-diabetes is associated with future diabetes, cardiovascular disease and the all cause mortality rate [28]. Preventive treatment with metformin has been initiated during these very early disease stages in obese adolescents [29].

Another example is hypertension (a disease), which is defined arbitrarily as blood pressure (BP) above 140/90 mmHg. Pre-hypertension (or borderline hypertension) is defined as BP below 140/90 mmHg but higher than 120/80 mmHg. BP tends to increase with age, and those whose BP has not yet reached 140/90 (disease), or even 120/80 (pre-disease), may still have higher BP than they did when they were younger [30]. Mortality is associated with BP, even if it is lower than 140/90 [31]. Both pre-hypertension and pre-diabetes are age-related pre-diseases. Likewise, the asymptomatic stages of Alzheimer's disease are also pre-disease.

In pre-diseases, abnormalities have not reached the arbitrary diagnostic criteria of the diseases. So, aging consists of progression from (pre)-pre-diseases (early aging) to diseases (late aging associated with functional decline). Aging is NOT a risk factor for these diseases, as aging consists of these diseases: aging and diseases are inseparable (Figure 1).

An aged appearance (e.g., grey hair, wrinkles, cushingoid body types and loss of muscles) are manifestations of pre-diseases. For example, an aged appearance may reflect hypercortisolism, sarcopenia, osteoporosis, skin pre-diseases and so on. And age-related skin lesions may herald pre-cancerous skin conditions [32].

What is "healthy" aging?

What then is aging without diseases, so called "healthy" aging. "Healthy" aging has been called subclinical aging [33], slow aging [18, 34] or decelerated aging [35], during which diseases are at the pre-disease or even pre-pre-disease stage. Diseases will spring up eventually. "Healthy" aging is a pre-disease state in which asymptomatic abnormalities have not yet reached the artificial definitions of diseases such as hypertension or diabetes. Instead of healthy aging, we could use the terms pre-disease aging or decelerated aging. Furthermore, decelerated aging can be achieved pharmacologically. For example, rapamycin decelerates aging, thereby making one healthier [36, 37].

Currently, the term healthspan lacks clarity and precision especially in animals [38]. Although the duration of healthspan depends on arbitrary criteria and subjective self-rating, it is a useful abstraction. In theory, a treatment that slows aging increases both healthspan (subclinical period) and lifespan, whereas a treatment that increases lifespan (e.g., coronary bypass, defibrillation) is not necessarily increase healthspan (Figure 1 in reference [33]). The goal of both anti-aging therapies and preventive medicine is to extend healthspan (by preventing diseases), thus extending total lifespan.

Preventive medicine: a step towards anti-aging medicine

Aging is the sum of diseases and pre-diseases. Treatments are generally more effective at pre-disease stages, associated with hyper-function, than at disease stages, associated with functional decline. As discussed in 2006, "rapamycin will prevent diseases rather than cure complications of diseases. For example, rapamycin

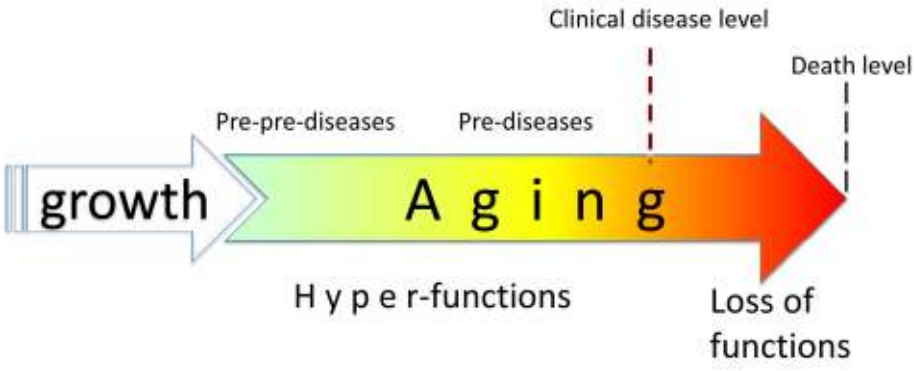

Figure 1. Relationship between aging and diseases. When growth is completed, growth-promoting pathways increase cellular and systemic functions and thus drive aging. This is a pre-pre-disease stage, slowly progressing to a pre-disease stage. Eventually, alterations reach clinical disease definition, associated with organ damage, loss of functions (functional decline), rapid deterioration and death.

will not repair broken bones but might prevent osteoporosis." [10]. In fact, rapamycin prevents osteoporosis [39].

The goal of preventive medicine is to prevent diseases by treating pre-diseases. Thus, preventive medicine is a form of anti-aging therapy. Both preventive medicine and anti-aging therapy should prevent pre-diseases by treating "healthy" individuals. Some of the drugs used in preventive medicine include statins, aspirin, ACE inhibitors (e.g., lisinopril) and metformin, which can be repurposed as anti-aging drugs [40, 41]. And *vice versa*, rapamycin, an anti-aging drug, may become a cornerstone of preventive medicine. As David Gems put it, "anti-aging treatment is any preventative approach to reduce late-life pathology. Its adoption would facilitate translation, since it would shift the emphasis to medical practice, particularly the introduction of preventative approaches." [42].

To treat what is treatable

The fact that aging is an obligatory part of the life of all organisms is not important. What is important is that aging is deadly and, most importantly, treatable. Consider an analogy. Is facial hair (beard) in males a disease? No of course, not. Still most men shave it, effectively "treating" this non-disease, simply because it is easily treatable. Is presbyopia (blurred near vision) a disease? It occurs in everyone by the age of 50 and is a continuation of developmental trends in the eye. It is treated as a disease because it is easily treatable with eye glasses. Unlike presbyopia, menopause in females is not usually treated because it is not easy to treat. Thus, the decision to treat or not to treat is often determined by whether it is possible to treat. It does not matter whether or not the target of treatment is called a disease.

Aging is treatable

As the simplest example, calorie restriction (CR) slows aging in diverse organisms, including primates [43-50]. Similarly, intermittent fasting (IF) and ketogenic diet (severe carbohydrate restriction) extend life span in mammals [48, 51-54]. CR (as well as carbohydrate restriction and IF fasting) improves health in humans [45, 48, 53, 55-62]. However, CR is unpleasant to most humans and its life-extending capacity is limited. Nutrients activate the mTOR (molecular Target of Rapamycin) nutrient-sensing pathway [63-65] and, as we will discuss mTOR drives aging, inhabitable by rapamycin. Rapamycin-based anti-aging therapies have been recently implemented by Dr. Alan Green (https://rapamycintherapy.com).

Rapamycin and other rapalogs

Rapamycin (Rapamune/Sirolimus), an allosteric inhibitor of mTOR complex 1 [63, 66], is a natural rapalog as well as the most potent and best studied rapalog. Rapamycin-analogs such as everolimus, temsirolimus (a rapamycin prodrug) and deforolimus/ Ridaforolimus are also now widely used.

Rapamycin, everolimus and deforolimus slow geroconversion [67-75]. It has been predicted that rapamycin would slow aging in mammals [10, 76]. Starting in 2009, numerous studies have demonstrated that rapamycin prolongs life in mice [75, 77-99], even when started late in life [77, 78, 97-99], or administrated transiently or intermittently [77, 88, 89, 95].

In these studies, rapamycin was most effective at high doses [88, 89, 93-96, 100-103]. Its effect and that of everolimus lingers after their discontinuation [104], even after a single dose [105]. What appears to be important is to reach high peak levels using a single high dose [93, 94].

In non-human primates, chronic and/or intermittent rapamycin improves metabolic functioning [106]. In a randomized controlled trial, middle-aged companion dogs administrated rapamycin exhibited no further side effects as compared to dogs receiving the placebo [107].

Millions of patients with various diseases and conditions (e.g., organ transplant recipients) have been treated with rapamycin (Sirolimus). Typical dose of rapamycin in organ-transplant patients is 2 mg/day. Rapamycin in a single dose of 15 mg was administrated to healthy volunteers without adverse effects [108]. Similarly, a dose of 8 mg/m2 (around 16 mg) was also well tolerated in healthy male volunteers [109]. What is amazing is that the placebo group reported more "side effects" such as astenia than did the rapamycin group [109]. In yet another study, comparison to placebo revealed no real everolimus-induced side effects in the elderly [104]. Moreover, everolimus improves immunity [110] and reduces infections in elderly healthy humans [104]. In placebo-controlled studies, side effects of rapamycin and everolimus are manageable with dose reduction and interruption. Discontinuation due to toxicity was uncommon [111]. In volunteers (aged 70-95 years, mean age of 80 years), treatment with 1mg/daily of rapamycin for 8 weeks was safe [112]. Matt Kaeberlein suggests that conventional doses of rapamycin maybe sub-optimal for maximum life-extension [113]. I agree with this opinion.

Conventional drugs as anti-aging drugs

Metformin is used not only to treat diabetes but also pre-diabetes in order to prevent diabetes [20-23]. Metformin decreases insulin-resistance and body weight and prevents diabetes, cancer and cardio-vascular disease [21, 22, 114-119]. It is expected that metformin would extend life and, in fact, metformin does decrease all-cause mortality [119, 120]. Physicians generally do not think of metformin as an anti-aging drug, simply because it is expected that life will be extended, if diseases are prevented. In mice, metformin extends healthspan and lifespan [117, 121-123]. It also extends the lifespan of *C. elegans* [124-127], which do not suffer from human diseases. Gerontologists think of metformin as an anti-aging drug [121-130], and metformin can be combined with rapamycin [131].

Angiotensin II inhibitors

Angiotensin-converting enzyme (ACE) inhibitors (e.g., Captopril, Lisinopril, Enalapril, Ramipril) and Angiotensin II receptor blockers (ARB) (e.g., Valsartan, Telmisartan, Losartan) are widely used to treat hypertension, which is a typical hyperfunctional disease. Vasoconstriction, cardiomyocyte hypertrophy, beta- and alpha- adrenergic hyperstimulation all lead to high blood pressure (systemic hyperfunction), which, in turn can contribute to stroke, myocardial infarction and renal failure. ACE inhibitors and ARBs decrease vasoconstriction and prevent cardiac hypertrophy. They are life-extending drugs because they treat deadly diseases.

Notably, ACE inhibitors increase the lifespan in rodents with normal blood pressure [132-134], thereby acting as anti-aging drugs.

Combinations of conventional drugs

Combinations of aspirin, statins, beta-blockers and ACE inhibitors are given to aging individuals to prevent cardiovascular diseases [135]. On the other hand, these drugs extend life span in rodents and Drosophila [136].

Typical combinations (polypill) include an antiplatelet agent (aspirin), a statin and two blood pressure-lowering drugs such as lisinopril and a beta-blocker [137,138]. Such combinations are estimated to reduce the 5-year incidence of stroke by 50% [139]. Aspirin, statins, ACE inhibitors, beta-blockers and metformin prevent some types of cancer and pre-cancerous polyps [116-118, 140-146].

Treating aging by preventing diseases or preventing diseases by slowing aging

As discussed, "aging is the sum of all age-related diseases" and this "sum is the best biomarker of aging" [17]. One could say that drugs prevent diseases by slowing aging. Alternatively, it could be said that prevention of diseases slows aging, which is the sum of all diseases and pre-diseases. If a drug prevents diseases, it will extend lifespan (apparently slowing down aging). If a drug slows down aging it will prevent diseases and extend healthspan [17, 147].

As suggested "narrow spectrum anti-aging treatments (e.g. the cardiovascular polypill) could establish a practice that eventually extends to broader spectrum anti-aging treatments (e.g. dietary restriction mimetics)". [42].

CONCLUSION

It is commonly argued that aging should be defined as a disease so as to accelerate development of anti-aging therapies. This attitude is self-defeating because it allows us to postpone development of anti-aging therapies until aging is pronounced a disease by regulatory bodies, which will not happen soon. Aging does not need to be defined as a disease to be treated. Anti-aging drugs such as rapamycin delay age-related diseases. If a drug does not delay progression of at least one age-related disease, it cannot possibly be considered as an anti-aging drug, because it will not extend life-span by definition (animals die from age-related diseases). It has been suggested [17], "in order to extend life span, an anti-aging drug must delay age-related diseases. … Once a drug is used for treatment of any one chronic disease, its effect against other diseases … may be evaluated in the same group of patients." Aging can be treated as a pre-disease to prevent its progression to diseases. Rapamycin-based combinations include conventional life-extending drugs, which are used to treat and prevent age-related diseases. These com-binations could be combined with modestly low-calorie/carbohydrates diet, physical exercise and stress avoidance [40, 41]. And this approach is actually being used now to treat aging at Alan Green's clinic in Little Neck, NY: http://roguehealthandfitness.com/rapamycin-anti-aging-medicine-an-interview-with-alan-s-green-m-d/?print=pdf and https://rapamycintherapy.com

CONFLICTS OF INTEREST

The author declares no conflicts of interest. The author did not participate in Editorial process.

REFERENCES

1. Bulterijs S, Hull RS, Björk VC, Roy AG. It is time to classify biological aging as a disease. Front Genet. 2015; 6:205. https://doi.org/10.3389/fgene.2015.00205

2. Caplan AL. Death as an unnatural process. Why is it wrong to seek a cure for aging? EMBO Rep. 2005; 6:S72–75. https://doi.org/10.1038/sj.embor.7400435

3. Gems D. The aging-disease false dichotomy: understanding senescence as pathology. Front Genet. 2015; 6:212. https://doi.org/10.3389/fgene.2015.00212

4. Zhavoronkov A, Bhullar B. Classifying aging as a disease in the context of ICD-11. Front Genet. 2015; 6:326. https://doi.org/10.3389/fgene.2015.00326

5. Stambler I. Recognizing Degenerative Aging as a Treatable Medical Condition: methodology and Policy. Aging Dis. 2017; 8:583–89. https://doi.org/10.14336/AD.2017.0130

6. Stambler I. Has aging ever been considered healthy? Front Genet. 2015; 6:202. https://doi.org/10.3389/fgene.2015.00202

7. Faragher RG. Should we treat aging as a disease? The consequences and dangers of miscategorisation. Front Genet. 2015; 6:171. https://doi.org/10.3389/fgene.2015.00171

8. Dilman VM, Revskoy SY, Golubev AG. Neuroendocrine-ontogenetic mechanism of aging: toward an integrated theory of aging. Int Rev Neurobiol. 1986; 28:89–156. https://doi.org/10.1016/S0074-7742(08)60107-5

9. Dilman VM. Four models of medicine. Medicina: Leningrad 1987.

10. Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle. 2006; 5:2087–102. https://doi.org/10.4161/cc.5.18.3288

11. Blagosklonny MV. Revisiting the antagonistic pleiotropy theory of aging: TOR-driven program and quasi-program. Cell Cycle. 2010; 9:3151–56. https://doi.org/10.4161/cc.9.16.13120

12. Blagosklonny MV. Aging is not programmed: genetic pseudo-program is a shadow of developmental growth. Cell Cycle. 2013; 12:3736–42. https://doi.org/10.4161/cc.27188

13. Gems D, Partridge L. Genetics of longevity in model organisms: debates and paradigm shifts. Annu Rev Physiol. 2013; 75:621–44. https://doi.org/10.1146/annurev-physiol-030212-183712

14. Gems D, de la Guardia Y. Alternative Perspectives on Aging in Caenorhabditis elegans: Reactive Oxygen Species or Hyperfunction? Antioxid Redox Signal. 2013; 19:321–29. https://doi.org/10.1089/ars.2012.4840

15. Wang H, Zhao Y, Ezcurra M, Benedetto A, Gilliat AF, Hellberg J, Ren Z, Galimov ER, Athigapanich T, Girstmair J, Telford MJ, Dolphin CT, Zhang Z, Gems D. A parthenogenetic quasi-program causes teratoma-like tumors during aging in wild-type *C. elegans.* NPJ Aging Mech Dis. 2018; 4:6. https://doi.org/10.1038/s41514-018-0025-3

16. Wang H, Zhang Z, Gems D. Monsters in the uterus: teratoma-like tumors in senescent *C. elegans* result from a parthenogenetic quasi-program. Aging (Albany NY). 2018; 10:1188–89. https://doi.org/10.18632/aging.101486

17. Blagosklonny MV. Validation of anti-aging drugs by treating age-related diseases. Aging (Albany NY). 2009; 1:281–88. https://doi.org/10.18632/aging.100034

18. Blagosklonny MV. Answering the ultimate question "what is the proximal cause of aging?". Aging (Albany NY). 2012; 4:861–77. https://doi.org/10.18632/aging.100525

19. Blagosklonny MV. TOR-centric view on insulin resistance and diabetic complications: perspective for endocrinologists and gerontologists. Cell Death Dis. 2013; 4:e964. https://doi.org/10.1038/cddis.2013.506

20. Hostalek U, Gwilt M, Hildemann S. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs. 2015; 75:1071–94. https://doi.org/10.1007/s40265-015-0416-8

21. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2012; 35:731–37. https://doi.org/10.2337/dc11-1299

22. Aroda VR, Knowler WC, Crandall JP, Perreault L, Edelstein SL, Jeffries SL, Molitch ME, Pi-Sunyer X, Darwin C, Heckman-Stoddard BM, Temprosa M, Kahn SE, Nathan DM, and Diabetes Prevention Program Research Group. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia. 2017; 60:1601–11. https://doi.org/10.1007/s00125-017-4361-9

23. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015; 3:866–75. https://doi.org/10.1016/S2213-8587(15)00291-0

24. Færch K, Vistisen D, Pacini G, Torekov SS, Johansen NB, Witte DR, Jonsson A, Pedersen O, Hansen T, Lauritzen T, Jørgensen ME, Ahrén B, Holst JJ. Insulin Resistance Is Accompanied by Increased Fasting Glucagon and Delayed Glucagon Suppression in Individuals With Normal and Impaired Glucose Regulation. Diabetes. 2016; 65:3473–81. https://doi.org/10.2337/db16-0240

25. Dankner R, Chetrit A, Shanik MH, Raz I, Roth J. Basal-state hyperinsulinemia in healthy normoglycemic adults is predictive of type 2 diabetes over a 24-year follow-up: a preliminary report. Diabetes Care. 2009; 32:1464–66. https://doi.org/10.2337/dc09-0153

26. Dankner R, Chetrit A, Shanik MH, Raz I, Roth J. Basal state hyperinsulinemia in healthy normoglycemic adults heralds dysglycemia after more than two decades of follow up. Diabetes Metab Res Rev. 2012; 28:618–24. https://doi.org/10.1002/dmrr.2322

27. Weir GC, Bonner-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes. 2004 (Suppl 3); 53:S16–21. https://doi.org/10.2337/diabetes.53.suppl_3.S16

28. Hulman A, Vistisen D, Glümer C, Bergman M, Witte DR, Færch K. Glucose patterns during an oral glucose tolerance test and associations with future diabetes, cardiovascular disease and all-cause mortality rate. Diabetologia. 2018; 61:101–07. https://doi.org/10.1007/s00125-017-4468-z

29. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 2001; 107:E55. https://doi.org/10.1542/peds.107.4.e55

30. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJNational Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289:2560–72. https://doi.org/10.1001/jama.289.19.2560

31. Huang Y, Su L, Cai X, Mai W, Wang S, Hu Y, Wu Y, Tang H, Xu D. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. Am Heart J. 2014; 167:160–168.e1. https://doi.org/10.1016/j.ahj.2013.10.023

32. Ollstein RN. Skin lesions in the elderly: precancer and cancer. Care Manag J. 2004; 5:107–11. https://doi.org/10.1891/cmaj.5.2.107.66279

33. Blagosklonny MV. How to save Medicare: the anti-aging remedy. Aging (Albany NY). 2012; 4:547–52. https://doi.org/10.18632/aging.100479

34. Blagosklonny MV. Why human lifespan is rapidly increasing: solving "longevity riddle" with "revealed-slow-aging" hypothesis. Aging (Albany NY). 2010; 2:177–82. https://doi.org/10.18632/aging.100139

35. Franceschi C, Garagnani P, Morsiani C, Conte M, Santoro A, Grignolio A, Monti D, Capri M, Salvioli S. The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. Front Med (Lausanne). 2018; 5:61. https://doi.org/10.3389/fmed.2018.00061

36. Blagosklonny MV. Rapamycin extends life- and health span because it slows aging. Aging (Albany NY). 2013; 5:592–98. https://doi.org/10.18632/aging.100591

37. Kaeberlein M. The Biology of Aging: Citizen Scientists and Their Pets as a Bridge Between Research on Model Organisms and Human Subjects. Vet Pathol. 2016; 53:291–98. https://doi.org/10.1177/0300985815591082

38. Kaeberlein M. How healthy is the healthspan concept? Geroscience. 2018; 40:361–64. https://doi.org/10.1007/s11357-018-0036-9

39. Luo D, Ren H, Li T, Lian K, Lin D. Rapamycin reduces severity of senile osteoporosis by activating osteocyte autophagy. Osteoporos Int. 2016; 27:1093–101. https://doi.org/10.1007/s00198-015-3325-5

40. Blagosklonny MV. Koschei the immortal and anti-aging drugs. Cell Death Dis. 2014; 5:e1552. https://doi.org/10.1038/cddis.2014.520

41. Blagosklonny MV. From rapalogs to anti-aging formula. Oncotarget. 2017; 8:35492–507. https://doi.org/10.18632/oncotarget.18033

42. Gems D. What is an anti-aging treatment? Exp Gerontol. 2014; 58:14–18. https://doi.org/10.1016/j.exger.2014.07.003

43. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science. 2009; 325:201–04.

https://doi.org/10.1126/science.1173635

44. Blagosklonny MV. Calorie restriction: decelerating mTOR-driven aging from cells to organisms (including humans). Cell Cycle. 2010; 9:683–88. https://doi.org/10.4161/cc.9.4.10766

45. Cava E, Fontana L. Will calorie restriction work in humans? Aging (Albany NY). 2013; 5:507–14. https://doi.org/10.18632/aging.100581

46. Mercken EM, Carboneau BA, Krzysik-Walker SM, de Cabo R. Of mice and men: the benefits of caloric restriction, exercise, and mimetics. Ageing Res Rev. 2012; 11:390–98. https://doi.org/10.1016/j.arr.2011.11.005

47. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun. 2014; 5:3557. https://doi.org/10.1038/ncomms4557

48. Trepanowski JF, Canale RE, Marshall KE, Kabir MM, Bloomer RJ. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. Nutr J. 2011; 10:107. https://doi.org/10.1186/1475-2891-10-107

49. Testa G, Biasi F, Poli G, Chiarpotto E. Calorie restriction and dietary restriction mimetics: a strategy for improving healthy aging and longevity. Curr Pharm Des. 2014; 20:2950–77. https://doi.org/10.2174/13816128113196660699

50. Ingram DK, Roth GS. Calorie restriction mimetics: can you have your cake and eat it, too? Ageing Res Rev. 2015; 20:46–62. https://doi.org/10.1016/j.arr.2014.11.005

51. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci. 2018; 19:63–80. https://doi.org/10.1038/nrn.2017.156

52. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 2017; 39:46–58. https://doi.org/10.1016/j.arr.2016.10.005

53. Xie K, Neff F, Markert A, Rozman J, Aguilar-Pimentel JA, Amarie OV, Becker L, Brommage R, Garrett L, Henzel KS, Hölter SM, Janik D, Lehmann I, et al. Every-other-day feeding extends lifespan but fails to delay many symptoms of aging in mice. Nat Commun. 2017; 8:155. https://doi.org/10.1038/s41467-017-00178-3

54. Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D, Perez G, Gutierrez-Casado E, Koike S, Knotts TA, Imai DM, Griffey SM, Kim K, et al. A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice. Cell Metab. 2017; 26:539–546.e5. https://doi.org/10.1016/j.cmet.2017.08.005

55. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. Ageing Res Rev. 2017; 39:36–45. https://doi.org/10.1016/j.arr.2016.08.005

56. Omodei D, Fontana L. Calorie restriction and prevention of age-associated chronic disease. FEBS Lett. 2011; 585:1537–42. https://doi.org/10.1016/j.febslet.2011.03.015

57. Lefevre M, Redman LM, Heilbronn LK, Smith JV, Martin CK, Rood JC, Greenway FL, Williamson DA, Smith SR. Ravussin E and team. ftPC. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. Atherosclerosis. 2009; 203:206-13. https://doi.org/10.1016/j.atherosclerosis.2008.05.036

58. Fontana L, Klein S, Holloszy JO. Effects of long-term calorie restriction and endurance exercise on glucose tolerance, insulin action, and adipokine production. Age (Dordr). 2010; 32:97–108. https://doi.org/10.1007/s11357-009-9118-z

59. Lettieri-Barbato D, Giovannetti E, Aquilano K. Effects of dietary restriction on adipose mass and biomarkers of healthy aging in human. Aging (Albany NY). 2016; 8:3341–55. https://doi.org/10.18632/aging.101122

60. Mattson MP, Wan R. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. J Nutr Biochem. 2005; 16:129–37. https://doi.org/10.1016/j.jnutbio.2004.12.007

61. Daly ME, Paisey R, Paisey R, Millward BA, Eccles C, Williams K, Hammersley S, MacLeod KM, Gale TJ. Short-term effects of severe dietary carbohydrate-restriction advice in Type 2 diabetes--a randomized controlled trial. Diabet Med. 2006; 23:15–20. https://doi.org/10.1111/j.1464-5491.2005.01760.x

62. Longo VD, Panda S. Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan. Cell Metab. 2016; 23:1048–59. https://doi.org/10.1016/j.cmet.2016.06.001

63. Wolfson RL, Sabatini DM. The Dawn of the Age of Amino Acid Sensors for the mTORC1 Pathway. Cell Metab. 2017; 26:301–09. https://doi.org/10.1016/j.cmet.2017.07.001

64. Shimobayashi M, Hall MN. Multiple amino acid sensing inputs to mTORC1. Cell Res. 2016; 26:7–20. https://doi.org/10.1038/cr.2015.146

65. Jewell JL, Guan KL. Nutrient signaling to mTOR and cell growth. Trends Biochem Sci. 2013; 38:233–42. https://doi.org/10.1016/j.tibs.2013.01.004

66. Thoreen CC, Kang SA, Chang JW, Liu Q, Zhang J, Gao Y, Reichling LJ, Sim T, Sabatini DM, Gray NS. An ATP-competitive mammalian target of rapamycin inhibitor reveals rapamycin-resistant functions of mTORC1. J Biol Chem. 2009; 284:8023–32. https://doi.org/10.1074/jbc.M900301200

67. Demidenko ZN, Blagosklonny MV. Growth stimulation leads to cellular senescence when the cell cycle is blocked. Cell Cycle. 2008; 7:3355–61. https://doi.org/10.4161/cc.7.21.6919

68. Iglesias-Bartolome R, Patel V, Cotrim A, Leelahavanichkul K, Molinolo AA, Mitchell JB, Gutkind JS. mTOR inhibition prevents epithelial stem cell senescence and protects from radiation-induced mucositis. Cell Stem Cell. 2012; 11:401–14. https://doi.org/10.1016/j.stem.2012.06.007

69. Kolesnichenko M, Hong L, Liao R, Vogt PK, Sun P. Attenuation of TORC1 signaling delays replicative and oncogenic RAS-induced senescence. Cell Cycle. 2012; 11:2391–401. https://doi.org/10.4161/cc.20683

70. Leontieva OV, Demidenko ZN, Blagosklonny MV. Contact inhibition and high cell density deactivate the mammalian target of rapamycin pathway, thus suppressing the senescence program. Proc Natl Acad Sci USA. 2014; 111:8832–37. https://doi.org/10.1073/pnas.1405723111

71. Leontieva OV, Blagosklonny MV. Gerosuppression by pan-mTOR inhibitors. Aging (Albany NY). 2016; 8:3535–51. https://doi.org/10.18632/aging.101155

72. Walters HE, Deneka-Hannemann S, Cox LS. Reversal of phenotypes of cellular senescence by pan-mTOR inhibition. Aging (Albany NY). 2016; 8:231–44. https://doi.org/10.18632/aging.100872

73. Wang R, Yu Z, Sunchu B, Shoaf J, Dang I, Zhao S, Caples K, Bradley L, Beaver LM, Ho E, Löhr CV, Perez VI. Rapamycin inhibits the secretory phenotype of senescent cells by a Nrf2-independent mechanism. Aging Cell. 2017; 16:564–74. https://doi.org/10.1111/acel.12587

74. Laberge RM, Sun Y, Orjalo AV, Patil CK, Freund A, Zhou L, Curran SC, Davalos AR, Wilson-Edell KA, Liu S, Limbad C, Demaria M, Li P, et al. MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. Nat Cell Biol. 2015; 17:1049–61. https://doi.org/10.1038/ncb3195

75. Christy B, Demaria M, Campisi J, Huang J, Jones D, Dodds SG, Williams C, Hubbard G, Livi CB, Gao X, Weintraub S, Curiel T, Sharp ZD, Hasty P. p53 and rapamycin are additive. Oncotarget. 2015; 6:15802–13. https://doi.org/10.18632/oncotarget.4602

76. Blagosklonny MV. Rapamycin and quasi-programmed aging: four years later. Cell Cycle. 2010; 9:1859–62. https://doi.org/10.4161/cc.9.10.11872

77. Chen C, Liu Y, Liu Y, Zheng P. mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. Sci Signal. 2009; 2:ra75. https://doi.org/10.1126/scisignal.2000559

78. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009; 460:392–95. https://doi.org/10.1038/nature08221

79. Anisimov VN, Zabezhinski MA, Popovich IG, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Antoch MP, Blagosklonny MV. Rapamycin extends maximal lifespan in cancer-prone mice. Am J Pathol. 2010; 176:2092–97. https://doi.org/10.2353/ajpath.2010.091050

80. Anisimov VN, Zabezhinski MA, Popovich IG, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Rosenfeld SV, Blagosklonny MV. Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice. Cell Cycle. 2011; 10:4230–36. https://doi.org/10.4161/cc.10.24.18486

81. Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ, Pletcher S, Sharp ZD, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. J Gerontol A Biol Sci Med Sci. 2011; 66:191–201. https://doi.org/10.1093/gerona/glq178

82. Wilkinson JE, Burmeister L, Brooks SV, Chan CC, Friedline S, Harrison DE, Hejtmancik JF, Nadon N, Strong R, Wood LK, Woodward MA, Miller RA. Rapamycin slows aging in mice. Aging Cell. 2012; 11:675–82. https://doi.org/10.1111/j.1474-9726.2012.00832.x

83. Comas M, Toshkov I, Kuropatwinski KK, Chernova OB, Polinsky A, Blagosklonny MV, Gudkov AV, Antoch MP. New nanoformulation of rapamycin Rapatar extends lifespan in homozygous p53-/- mice by delaying carcinogenesis. Aging (Albany NY). 2012; 4:715–22. https://doi.org/10.18632/aging.100496

84. Komarova EA, Antoch MP, Novototskaya LR, Chernova OB, Paszkiewicz G, Leontieva OV, Blagosklonny MV, Gudkov AV. Rapamycin extends lifespan and delays tumorigenesis in heterozygous p53+/- mice. Aging (Albany NY). 2012; 4:709–14.

https://doi.org/10.18632/aging.100498

85. Livi CB, Hardman RL, Christy BA, Dodds SG, Jones D, Williams C, Strong R, Bokov A, Javors MA, Ikeno Y, Hubbard G, Hasty P, Sharp ZD. Rapamycin extends life span of Rb1+/- mice by inhibiting neuroendocrine tumors. Aging (Albany NY). 2013; 5:100–10. https://doi.org/10.18632/aging.100533

86. Neff F, Flores-Dominguez D, Ryan DP, Horsch M, Schröder S, Adler T, Afonso LC, Aguilar-Pimentel JA, Becker L, Garrett L, Hans W, Hettich MM, Holtmeier R, et al. Rapamycin extends murine lifespan but has limited effects on aging. J Clin Invest. 2013; 123:3272–91. https://doi.org/10.1172/JCI67674

87. Fok WC, Chen Y, Bokov A, Zhang Y, Salmon AB, Diaz V, Javors M, Wood WH 3rd, Zhang Y, Becker KG, Pérez VI, Richardson A. Mice fed rapamycin have an increase in lifespan associated with major changes in the liver transcriptome. PLoS One. 2014; 9:e83988. https://doi.org/10.1371/journal.pone.0083988

88. Leontieva OV, Paszkiewicz GM, Blagosklonny MV. Weekly administration of rapamycin improves survival and biomarkers in obese male mice on high-fat diet. Aging Cell. 2014; 13:616–22. https://doi.org/10.1111/acel.12211

89. Miller RA, Harrison DE, Astle CM, Fernandez E, Flurkey K, Han M, Javors MA, Li X, Nadon NL, Nelson JF, Pletcher S, Salmon AB, Sharp ZD, et al. Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction. Aging Cell. 2014; 13:468–77. https://doi.org/10.1111/acel.12194

90. Popovich IG, Anisimov VN, Zabezhinski MA, Semenchenko AV, Tyndyk ML, Yurova MN, Blagosklonny MV. Lifespan extension and cancer prevention in HER-2/neu transgenic mice treated with low intermittent doses of rapamycin. Cancer Biol Ther. 2014; 15:586–92. https://doi.org/10.4161/cbt.28164

91. Siegmund SE, Yang H, Sharma R, Javors M, Skinner O, Mootha V, Hirano M, Schon EA. Low-dose rapamycin extends lifespan in a mouse model of mtDNA depletion syndrome. Hum Mol Genet. 2017; 26:4588–605. https://doi.org/10.1093/hmg/ddx341

92. Khapre RV, Kondratova AA, Patel S, Dubrovsky Y, Wrobel M, Antoch MP, Kondratov RV. BMAL1-dependent regulation of the mTOR signaling pathway delays aging. Aging (Albany NY). 2014; 6:48–57. https://doi.org/10.18632/aging.100633

93. Johnson SC, Yanos ME, Kayser EB, Quintana A, Sangesland M, Castanza A, Uhde L, Hui J, Wall VZ, Gagnidze A, Oh K, Wasko BM, Ramos FJ, et al. mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome. Science. 2013; 342:1524–28. https://doi.org/10.1126/science.1244360

94. Johnson SC, Yanos ME, Bitto A, Castanza A, Gagnidze A, Gonzalez B, Gupta K, Hui J, Jarvie C, Johnson BM, Letexier N, McCanta L, Sangesland M, et al. Dose-dependent effects of mTOR inhibition on weight and mitochondrial disease in mice. Front Genet. 2015; 6:247. https://doi.org/10.3389/fgene.2015.00247

95. Bitto A, Ito TK, Pineda VV, LeTexier NJ, Huang HZ, Sutlief E, Tung H, Vizzini N, Chen B, Smith K, Meza D, Yajima M, Beyer RP, et al. Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. eLife. 2016; 5:5. https://doi.org/10.7554/eLife.16351

96. Johnson SC, Kaeberlein M. Rapamycin in aging and disease: maximizing efficacy while minimizing side effects. Oncotarget. 2016; 7:44876–78. https://doi.org/10.18632/oncotarget.10381

97. Flynn JM, O'Leary MN, Zambataro CA, Academia EC, Presley MP, Garrett BJ, Zykovich A, Mooney SD, Strong R, Rosen CJ, Kapahi P, Nelson MD, Kennedy BK, Melov S. Late-life rapamycin treatment reverses age-related heart dysfunction. Aging Cell. 2013; 12:851–62. https://doi.org/10.1111/acel.12109

98. Ye L, Widlund AL, Sims CA, Lamming DW, Guan Y, Davis JG, Sabatini DM, Harrison DE, Vang O, Baur JA. Rapamycin doses sufficient to extend lifespan do not compromise muscle mitochondrial content or endurance. Aging (Albany NY). 2013; 5:539–50. https://doi.org/10.18632/aging.100576

99. Dai DF, Karunadharma PP, Chiao YA, Basisty N, Crispin D, Hsieh EJ, Chen T, Gu H, Djukovic D, Raftery D, Beyer RP, MacCoss MJ, Rabinovitch PS. Altered proteome turnover and remodeling by short-term caloric restriction or rapamycin rejuvenate the aging heart. Aging Cell. 2014; 13:529–39. https://doi.org/10.1111/acel.12203

100. Felici R, Buonvicino D, Muzzi M, Cavone L, Guasti D, Lapucci A, Pratesi S, De Cesaris F, Luceri F, Chiarugi A. Post onset, oral rapamycin treatment delays development of mitochondrial encephalopathy only at supramaximal doses. Neuropharmacology. 2017; 117:74–84. https://doi.org/10.1016/j.neuropharm.2017.01.039

101. Li A, Fan S, Xu Y, Meng J, Shen X, Mao J, Zhang L, Zhang X, Moeckel G, Wu D, Wu G, Liang C. Rapamycin treatment dose-dependently improves the cystic kidney in a new ADPKD mouse model via the mTORC1 and cell-cycle-associated CDK1/cyclin axis. J Cell Mol Med. 2017; 21:1619–35. https://doi.org/10.1111/jcmm.13091

102. Leontieva OV, Paszkiewicz GM, Blagosklonny MV.

Comparison of rapamycin schedules in mice on high-fat diet. Cell Cycle. 2014; 13:3350–56. https://doi.org/10.4161/15384101.2014.970491

103. Leontieva OV, Paszkiewicz GM, Blagosklonny MV. Fasting levels of hepatic p-S6 are increased in old mice. Cell Cycle. 2014; 13:2656–59. https://doi.org/10.4161/15384101.2014.949150

104. Mannick JB, Morris M, Hockey HP, Roma G, Beibel M, Kulmatycki K, Watkins M, Shavlakadze T, Zhou W, Quinn D, Glass DJ, Klickstein LB. TORC1 inhibition enhances immune function and reduces infections in the elderly. Sci Transl Med. 2018; 10:eaaq1564. https://doi.org/10.1126/scitranslmed.aaq1564

105. Hebert M, Licursi M, Jensen B, Baker A, Milway S, Malsbury C, Grant VL, Adamec R, Hirasawa M, Blundell J. Single rapamycin administration induces prolonged downward shift in defended body weight in rats. PLoS One. 2014; 9:e93691. https://doi.org/10.1371/journal.pone.0093691

106. Ross C, Salmon A, Strong R, Fernandez E, Javors M, Richardson A, Tardif S. Metabolic consequences of long-term rapamycin exposure on common marmoset monkeys (Callithrix jacchus). Aging (Albany NY). 2015; 7:964–73. https://doi.org/10.18632/aging.100843

107. Urfer SR, Kaeberlein TL, Mailheau S, Bergman PJ, Creevy KE, Promislow DE, Kaeberlein M. A randomized controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs. Geroscience. 2017; 39:117–27. https://doi.org/10.1007/s11357-017-9972-z

108. Tortorici MA, Parks V, Matschke K, Korth-Bradley J, Patat A. The evaluation of potential pharmacokinetic interaction between sirolimus and tacrolimus in healthy volunteers. Eur J Clin Pharmacol. 2013; 69:835–42. https://doi.org/10.1007/s00228-012-1407-2

109. Brattström C, Säwe J, Jansson B, Lönnebo A, Nordin J, Zimmerman JJ, Burke JT, Groth CG. Pharmacokinetics and safety of single oral doses of sirolimus (rapamycin) in healthy male volunteers. Ther Drug Monit. 2000; 22:537–44. https://doi.org/10.1097/00007691-200010000-00006

110. Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, Glass DJ, Klickstein LB. mTOR inhibition improves immune function in the elderly. Sci Transl Med. 2014; 6:268ra179. https://doi.org/10.1126/scitranslmed.3009892

111. Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, Noguchi S, Perez A, Rugo HS, Deleu I, Burris HA 3rd, Provencher L, Neven P, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol. 2014; 25:2357–62. https://doi.org/10.1093/annonc/mdu456

112. Kraig E, Linehan LA, Liang H, Romo TQ, Liu Q, Wu Y, Benavides AD, Curiel TJ, Javors MA, Musi N, Chiodo L, Koek W, Gelfond JA, Kellogg DL Jr. A randomized control trial to establish the feasibility and safety of rapamycin treatment in an older human cohort: Immunological, physical performance, and cognitive effects. Exp Gerontol. 2018; 105:53–69. https://doi.org/10.1016/j.exger.2017.12.026

113. Kaeberlein M. Rapamycin and ageing: when, for how long, and how much? J Genet Genomics. 2014; 41:459–63. https://doi.org/10.1016/j.jgg.2014.06.009

114. Romero R, Erez O, Hüttemann M, Maymon E, Panaitescu B, Conde-Agudelo A, Pacora P, Yoon BH, Grossman LI. Metformin, the aspirin of the 21st century: its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity. Am J Obstet Gynecol. 2017; 217:282–302. https://doi.org/10.1016/j.ajog.2017.06.003

115. Goldberg RB, Aroda VR, Bluemke DA, Barrett-Connor E, Budoff M, Crandall JP, Dabelea D, Horton ES, Mather KJ, Orchard TJ, Schade D, Watson K, Temprosa M, and Diabetes Prevention Program Research Group. Effect of Long-Term Metformin and Lifestyle in the Diabetes Prevention Program and Its Outcome Study on Coronary Artery Calcium. Circulation. 2017; 136:52–64. https://doi.org/10.1161/CIRCULATIONAHA.116.025483

116. Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer Discov. 2012; 2:778–90. https://doi.org/10.1158/2159-8290.CD-12-0263

117. Anisimov VN. Metformin for cancer and aging prevention: is it a time to make the long story short? Oncotarget. 2015; 6:39398–407. https://doi.org/10.18632/oncotarget.6347

118. Heckman-Stoddard BM, DeCensi A, Sahasrabuddhe VV, Ford LG. Repurposing metformin for the prevention of cancer and cancer recurrence. Diabetologia. 2017; 60:1639–47. https://doi.org/10.1007/s00125-017-4372-6

119. Haukka J, Niskanen L, Auvinen A. Risk of Cause-Specific Death in Individuals with Cancer-Modifying Role Diabetes, Statins and Metformin. Int J Cancer. 2017; 141:2437–49.

https://doi.org/10.1002/ijc.31016

120. Gosmanova EO, Canada RB, Mangold TA, Rawls WN, Wall BM. Effect of metformin-containing antidiabetic regimens on all-cause mortality in veterans with type 2 diabetes mellitus. Am J Med Sci. 2008; 336:241–47. https://doi.org/10.1097/MAJ.0b013e31816250e6

121. Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, Zabezhinski MA, Tyndyk ML, Yurova MV, Kovalenko IG, Poroshina TE, Semenchenko AV. Metformin slows down aging and extends life span of female SHR mice. Cell Cycle. 2008; 7:2769–73. https://doi.org/10.4161/cc.7.17.6625

122. Anisimov VN, Berstein LM, Popovich IG, Zabezhinski MA, Egormin PA, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Kovalenko IG, Poroshina TE. If started early in life, metformin treatment increases life span and postpones tumors in female SHR mice. Aging (Albany NY). 2011; 3:148–57. https://doi.org/10.18632/aging.100273

123. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M, Pollak M, Zhang Y, et al. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013; 4:2192. https://doi.org/10.1038/ncomms3192

124. Cabreiro F, Au C, Leung KY, Vergara-Irigaray N, Cochemé HM, Noori T, Weinkove D, Schuster E, Greene ND, Gems D. Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism. Cell. 2013; 153:228–39. https://doi.org/10.1016/j.cell.2013.02.035

125. Wu L, Zhou B, Oshiro-Rapley N, Li M, Paulo JA, Webster CM, Mou F, Kacergis MC, Talkowski ME, Carr CE, Gygi SP, Zheng B, Soukas AA. An Ancient, Unified Mechanism for Metformin Growth Inhibition in C. elegans and Cancer. Cell. 2016; 167:1705–1718.e13. https://doi.org/10.1016/j.cell.2016.11.055

126. Chen J, Ou Y, Li Y, Hu S, Shao LW, Liu Y. Metformin extends *C. elegans* lifespan through lysosomal pathway. eLife. 2017; 6:6. https://doi.org/10.7554/eLife.31268

127. De Haes W, Frooninckx L, Van Assche R, Smolders A, Depuydt G, Billen J, Braeckman BP, Schoofs L, Temmerman L. Metformin promotes lifespan through mitohormesis via the peroxiredoxin PRDX-2. Proc Natl Acad Sci USA. 2014; 111:E2501–09. https://doi.org/10.1073/pnas.1321776111

128. Anisimov VN. Metformin for aging and cancer prevention. Aging (Albany NY). 2010; 2:760–74. https://doi.org/10.18632/aging.100230

129. Anisimov VN. Metformin: do we finally have an anti-aging drug? Cell Cycle. 2013; 12:3483–89. https://doi.org/10.4161/cc.26928

130. Pietrocola F, Kroemer G. Metformin: a metabolic modulator. Oncotarget. 2017; 8:9017–20. https://doi.org/10.18632/oncotarget.14794

131. Weiss R, Fernandez E, Liu Y, Strong R, Salmon AB. Metformin reduces glucose intolerance caused by rapamycin treatment in genetically heterogeneous female mice. Aging (Albany NY). 2018; 10: 386-401. https://doi.org/10.18632/aging.101401

132. Santos EL, de Picoli Souza K, da Silva ED, Batista EC, Martins PJ, D'Almeida V, Pesquero JB. Long term treatment with ACE inhibitor enalapril decreases body weight gain and increases life span in rats. Biochem Pharmacol. 2009; 78:951–58. https://doi.org/10.1016/j.bcp.2009.06.018

133. Spindler SR, Mote PL, Flegal JM. Combined statin and angiotensin-converting enzyme (ACE) inhibitor treatment increases the lifespan of long-lived F1 male mice. Age (Dordr). 2016; 38:379–91. https://doi.org/10.1007/s11357-016-9948-4

134. Basso N, Cini R, Pietrelli A, Ferder L, Terragno NA, Inserra F. Protective effect of long-term angiotensin II inhibition. Am J Physiol Heart Circ Physiol. 2007; 293:H1351–58. https://doi.org/10.1152/ajpheart.00393.2007

135. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, Gillman MW, Kemper AR, Krist AH, Kurth AE, Landefeld CS, LeFevre ML, Mangione CM, et al, and US Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016; 316:1997–2007. https://doi.org/10.1001/jama.2016.15450

136. Spindler SR, Mote PL, Li R, Dhahbi JM, Yamakawa A, Flegal JM, Jeske DR, Li R, Lublin AL. β1-Adrenergic receptor blockade extends the life span of Drosophila and long-lived mice. Age (Dordr). 2013; 35:2099–109. https://doi.org/10.1007/s11357-012-9498-3

137. Lafeber M, Spiering W, van der Graaf Y, Nathoe H, Bots ML, Grobbee DE, Visseren FL. The combined use of aspirin, a statin, and blood pressure-lowering agents (polypill components) and the risk of vascular morbidity and mortality in patients with coronary artery disease. Am Heart J. 2013; 166:282–289.e1. https://doi.org/10.1016/j.ahj.2013.04.011

138. Patel A, Cass A, Peiris D, Usherwood T, Brown A, Jan S, Neal B, Hillis GS, Rafter N, Tonkin A, Webster R, Billot L, Bompoint S, et al, and Kanyini Guidelines

Adherence with the Polypill (Kanyini GAP) Collaboration. A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk. Eur J Prev Cardiol. 2015; 22:920–30. https://doi.org/10.1177/2047487314530382

139. Brainin M, Feigin V, Martins S, Matz K, Roy J, Sandercock P, Teuschl Y, Tuomilehto J, Wiseman A. Cut stroke in half: polypill for primary prevention in stroke. Int J Stroke. 2018; 13:633–47. https://doi.org/10.1177/1747493018761190

140. Gronich N, Rennert G. Beyond aspirin-cancer prevention with statins, metformin and bisphosphonates. Nat Rev Clin Oncol. 2013; 10:625–42. https://doi.org/10.1038/nrclinonc.2013.169

141. Holmes MD, Chen WY. Hiding in plain view: the potential for commonly used drugs to reduce breast cancer mortality. Breast Cancer Res. 2012; 14:216. https://doi.org/10.1186/bcr3336

142. Kedika R, Patel M, Pena Sahdala HN, Mahgoub A, Cipher D, Siddiqui AA. Long-term use of angiotensin converting enzyme inhibitors is associated with decreased incidence of advanced adenomatous colon polyps. J Clin Gastroenterol. 2011; 45:e12–16. https://doi.org/10.1097/MCG.0b013e3181ea1044

143. Powe DG, Voss MJ, Zänker KS, Habashy HO, Green AR, Ellis IO, Entschladen F. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget. 2010; 1:628–38. https://doi.org/10.18632/oncotarget.101009

144. Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol. 2011; 29:2635–44. https://doi.org/10.1200/JCO.2010.33.5422

145. Thorat MA, Cuzick J. Role of aspirin in cancer prevention. Curr Oncol Rep. 2013; 15:533–40. https://doi.org/10.1007/s11912-013-0351-3

146. Blagosklonny MV. Prevention of cancer by inhibiting aging. Cancer Biol Ther. 2008; 7:1520–24. https://doi.org/10.4161/cbt.7.10.6663

147. Blagosklonny MV. Prospective treatment of age-related diseases by slowing down aging. Am J Pathol. 2012; 181:1142–46. https://doi.org/10.1016/j.ajpath.2012.06.024