
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

# The potential of rapalogs to enhance resilience against SARS-CoV-2 infection and reduce the severity of COVID-19

*Evelyne Bischof*, Richard C Siow*, Alex Zhavoronkov, Matt Kaeberlein*

**COVID-19 disproportionately affects older people, with likelihood of severe complications and death mirroring that of other age-associated diseases. Inhibition of the mechanistic target of rapamycin complex 1 (mTORC1) has been shown to delay or reverse many age-related phenotypes, including declining immune function. Rapamycin (sirolimus) and rapamycin derivatives are US Food and Drug Administration-approved inhibitors of mTORC1 with broad clinical utility and well established dosing and safety profiles. Based on preclinical and clinical evidence, a strong case can be made for immediate large-scale clinical trials to assess whether rapamycin and other mTORC1 inhibitors can prevent COVID-19 infection in these populations and also to determine whether these drugs can improve outcomes in patients with severe COVID-19.**

*Lancet Healthy Longev* 2021; 2: e105–11

*Contributed equally

**Shanghai University of Medicine & Health Sciences, School of Clinical Medicine, Shanghai, China** (E Bischof MD); **Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy** (E Bischof); **Ageing Research at King's and School of Cardiovascular Medicine & Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK** (R C Siow PhD); **Insilico Medicine, Hong Kong Special Administrative Region, China** (A Zhavoronkov PhD); **The Buck Institute for Research on Aging, Novato, CA, USA** (A Zhavoronkov); **Healthy Aging and Longevity Research Institute, Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA** (Prof M Kaeberlein PhD)

Correspondence to:
Prof M Kaeberlein, Healthy Aging and Longevity Research Institute, Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA 98195, USA
**kaeber@uw.edu**

See **Online** for appendix

## Introduction

The first case of infection caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, in December, 2019. On March 11, 2020, WHO declared COVID-19 a global pandemic. Since then, COVID-19 has affected the lives of billions of people; as of December, 2020, it is estimated that nearly 65 million people have been infected with and 1·8 million have died of COVID-19. After the rate of new infections and deaths plateaued after the first wave, the infection incidence is currently rapidly increasing again, as are concerns regarding the ongoing second wave and potential further waves, and the long-term effects following infection and recovery. Globally, we are observing geographical re-distribution of hotspots and are faced with the distinct possibility that outbreaks could reoccur not only in the months, but perhaps years ahead.

Similar to other viral infections, such as influenza, older people (eg, ≥65 years) are at a substantially increased risk of suffering adverse outcomes from COVID-19.[1] Although it remains too early to know the extent to which age affects the risk of initial infection, it is clear that age is by far the greatest risk factor for severe COVID-19 complications and death. Data from the US Centers for Disease Control and Prevention reveal that the risk of dying from COVID-19 increases approximately 10-fold for every 20 years of age.[2] This association between age and risk of COVID-19 mortality is comparable with the relationship between age and risk of death from Alzheimer's disease.[3]

We have postulated that the relationship between chronological age and COVID-19 mortality is driven primarily by the biological mechanisms of ageing,[2] a concept which has recently become more widely appreciated among clinicians and researchers.[4] At the cellular and molecular levels, these mechanisms have been described as the hallmarks[5] or pillars[6] of ageing. Previous research has revealed that these hallmarks can be directly linked to the age-associated loss of immune function concomitant with increases in systemic inflammation (also referred to as inflammaging).[7] Inflammaging can been seen in the form of aberrant activation of innate immune mechanisms, such as elevation of pro-inflammatory cytokines and increased numbers of natural killer cells,[8] with such activation exacerbating the increased risk of viral and bacterial infections that are associated with age. Impairment of immune function could also contribute to additional age-associated problems, including increased prevalence of autoimmune disorders and increased risk for numerous types of cancer due to impaired immune surveillance.[9,10]

The immune system loses efficacy with age.[9] Immunosenescence affects both innate and acquired immunity and greatly reduces the production of naive T-cells and B-cells in the thymus and bone marrow. Consequently, decreased antibody production leads to fewer T cell and B cell interactions, and a reduced release of thyroid hormones, thus leading to decreased natural killer cell activity and a functional decline in the body's ability to mount an immune response.[7] Older people are known to have a chronic low-threshold proinflammatory status along with elevated plasma markers (eg, interleukin-6, tumour necrosis factor-α, and C-reactive protein) in the absence of clinical symptoms.[8] On a cellular level, this translates to enhanced inflammatory activity, especially in monocytes and macrophages (ie, the innate immune system) that work to reciprocally enforce the ongoing inflammaging processes.[9]

The collective outcome is a compromised immune response and an increased incidence of inflammatory comorbidities—eg, cancers and age-related neurodegeneration, which further weaken the immune system.[10–13] The innate immune system, which is primarily involved in the response to new infections, is also compromised due to a reduction in clonal diversity.[14] This reciprocal relationship between inflammaging and immunosenescence is believed to underlie the adaptive processes, which exacerbates the severity of symptoms in older individuals who tend to exhibit an enhanced susceptibility towards infections along with a diminished response to vaccines.[15–17] Therefore, we and others propose that novel and effective strategies for combating COVID-19 can be developed by directly targeting the hallmarks of ageing to prevent or diminish inflammaging and immunosenescence.[2,11,12]

## mTOR inhibition increases lifespan and health in preclinical research

Studies investigating the mechanistic target of rapamycin (mTOR) pathway have shown that immunosenescence can be reversed by targeting biological ageing.[13,14] The mTOR protein is a nutrient-responsive and stress-responsive kinase that functions as a conserved regulator of ageing in eukaryotes.[14,15] Activation of mTOR promotes development and growth,[16,17] whereas genetic inhibition of mTOR increases lifespan in yeast,[18,19] nematodes,[20] fruit flies,[21] and mice.[22] The mTOR kinase acts in two distinct protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2).[23] In the context of biological ageing, inhibition of mTORC1 is consistently associated with increased lifespan, whereas inhibition of mTORC2 is associated with reduced lifespan, at least in mice.[24] mTORC1 regulates several key homoeostatic processes including autophagy, mRNA translation, and metabolism, each of which affects the hallmarks of ageing and, therefore, the lifespan of different model organisms.[25]

The macrolide antibiotic rapamycin (sirolimus) is an allosteric inhibitor of mTORC1 that acts by binding to the FK506 binding protein (FKBP12).[26–28] Similar to genetic inhibition of mTORC1, rapamycin has been shown to increase lifespan in yeast,[19] nematode worms,[29] fruit flies,[30] and mice.[31] The effects of rapamycin on lifespan have shown to be robust in mice, with lifespan extension being reported in multiple strain backgrounds across a broad dose range, involving both oral delivery and intraperitoneal injection.[31–41] Lifespan extension is comparable when treatment is initiated at young age,[41] in mid-life,[31] or transiently in late life.[40] Intermittent treatment with rapamycin in late life has also been shown to be effective at extending lifespan.[42] Importantly, the effects of rapamycin extend beyond increasing lifespan in mice, with evidence of reduction in hallmarks of ageing. These effects include fewer age-related cancers,[32,43] protection against cognitive decline,[44,45] improved cardiovascular function,[46–48] restoration of immune function,[49] and improved renal function,[50] oral health,[51,52] intestinal function and reduced gut dysbiosis,[40,53] and preserved ovarian function.[54]

Other pharmacological inhibitors of mTOR have been described but there is relatively little data on their effects on lifespan or health during ageing. In general, existing mTOR inhibitors can be classified into three categories: rapamycin derivatives (rapalogs), other mTORC1-specific inhibitors not structurally related to rapamycin, and ATP-competitive inhibitors of mTOR. Rapalogs and other mTORC1-specific inhibitors are generally predicted to function similarly to rapamycin in enhancing lifespan and improving age-related phenotypes;[55] however, only everolimus (known as RAD001) has been studied in this context. The evidence supporting geroprotective effects from everolimus include improved muscle function during ageing in rats[50] and improved immune function in healthy older people.[56,57] ATP-competitive inhibitors, which inhibit mTORC1 and mTORC2, usually have off-target effects on other kinases.[58] Examples of ATP-competitive inhibitors of mTOR include Torin 1, Torin 2, and the PI3K/mTOR dual kinase inhibitors such as dactolisib (known as BEZ235 or RTB101).[59–61] To our knowledge, there are scarce data supporting the positive effects of ATP-competitive mTOR inhibitors on lifespan in any research done in animals and only rapamycin has been shown to increase lifespan in mice.

## Inhibition of mTOR reverses age-related decline in immune function

Although rapamycin and rapalogs have usually been considered immunosuppressives, multiple studies have shown that rapalog monotherapy is sufficient to reverse age-related declines in immune function in mice and people. One of the first studies to show the effectiveness of rapalogs was done using research done in mice that investigated age-related immune senescence.[49] In that study, aged mice (aged 22–24 months) were treated with either rapamycin or a vehicle control for a period of 6 weeks. After a 2-week washout period, mice in each group were immunised against H1N1 influenza. 2 weeks later, both groups were challenged with live H1N1 and their survival was quantified. When compared with young immunised mice (aged 2 months), the aged mice that did not receive rapamycin showed a substantial reduction in response to the vaccine, with approximately two-thirds of the mice failing to mount an immune response and dying within 10 days of H1N1 challenge.[49] By contrast, aged mice that received rapamycin exhibited improved immune function, with all of the rapamycin-treated mice responding to the vaccine and surviving the subsequent H1N1 challenge past the endpoint of the experiment. This functional rejuvenation was associated with a decrease in senescence markers in haematopoietic stem cells along with improved stem-cell function,[49] although the precise mechanism of action remains to be established.

This preclinical work spurred efforts to assess whether similar outcomes would be seen in a clinical setting. Two phase 2 clinical trials have been completed in which older healthy adults were treated with everolimus alone[56] or everolimus combined with RTB10157 for 6 weeks. Both studies were randomised, placebo-controlled and found that patients who were given the rapalog showed improved responses to influenza vaccine when compared with those who received the placebo only. In the study using a combined treatment,[57] patients who received everolimus plus RTB101 also had fewer infections over the following year, suggesting that the immune-boosting effect might extend beyond the initial vaccine response. Enhanced autophagy because of mTOR inhibition along with increased expression of anti-viral proteins have been proposed as potential mechanisms of action for the observed immune-boosting effects in people. However, a subsequent phase 3 clinical trial using RTB101 alone did not meet its endpoint.

The observation that immune function can be improved over a period of several weeks to months following a single 6-week interval of mTORC1 inhibition has important clinical implications. Influenza alone is estimated to result in 300 000 to 500 000 deaths annually, with older individuals at highest risk.[62,63] Improving vaccine response among this susceptible population could substantially enhance preventive measures and reduce severe clinical outcomes. A transient treatment regimen is also likely to be more easily adopted across large cohorts and have substantially fewer adverse effects compared with chronic high-dose regimens adopted by organ transplant patients. Indeed, no clinically significant adverse events were noted in either of the phase 2 mTOR inhibitor trials,[56,57] and there is growing evidence that low-dose rapalog monotherapy has minimal side-effects in healthy older adults.[64,65] These findings are further supported by the absence of observed side-effects in non-human primate marmosets[66] and in older companion dogs[67,68] treated with lower doses of rapamycin.

A restoration of immune function in older adults is likely to have benefits that extend beyond simply boosting the response to an influenza vaccine. Before COVID-19, respiratory infections were estimated to account for more than 1 million deaths in adults older than 70 years and more than 2 million deaths in people of all ages annually worldwide,[69] numbers that were much higher in 2020. Additionally, it is expected that enhanced immune function would lead to reduced rates of age-associated cancers, as immune surveillance is known to be a crucial anti-cancer mechanism that is impaired by the aging process.[10] Reversion of age-related changes in the microbiome could also be expected following mTOR inhibition, as the immune system plays an important role in maintaining a healthy microbiome.[70] Rapamycin has been found to reduce age-related cancers[32,41] and modify the aged microbiome in mice,[40,51] although it remains to be established whether these effects are mediated by the immune system.

## Evaluating the feasibility of rapamycin for COVID-19 prevention

The most important consideration for any clinical intervention is to evaluate the potential benefit against the potential risk. This evaluation is always challenging to quantify but is even more difficult for a preventive treatment that is given to individuals who are not currently sick. As discussed, the potential benefits of preventing immunosenescence in older people are quite large and include reductions in morbidity and mortality from infectious disease and cancer. Regarding COVID-19, extrapolation from preclinical studies suggests that the immune restorative properties of rapamycin might be expected to reduce COVID-19 deaths substantially in the absence of a vaccine[2] and possibly by an even greater amount once a vaccine is widely available.

Because there are abundant clinical data on rapamycin use, we can also predict the potential risks. Rapamycin and other rapalogs (ie, everolimus, temsirolimus) have been widely used to prevent organ transplant rejection but are also approved for use in lymphangioleiomyomatosis, coronary stenting, and particular types of cancer (eg, hormone receptor positive breast cancer or neuroendocrine tumours.[71,72] Use of high-dose rapamycin (>15–25mg/kg) by organ transplant patients is associated with numerous side-effects including generalised pain (≥30% occurrence, leading to a 5% treatment discontinuation rate), headache, fever, hypertension, nausea, abdominal pain, constipation, diarrhoea, urinary tract infection, peripheral oedema, anaemia, arthralgia, thrombocytopenia, hypercholesterolaemia, hypertriglyceridemia, and increased creatinine.[73,74] Side-effects are mostly reversible and represent a worst-case scenario, as these patients are severely ill and taking high doses of the drug along with other

| | Recruitment status | Estimated enrolment | Study start date | Intervention group | Control group |
|---|---|---|---|---|---|
| Efficacy and safety of sirolimus in COVID-19 infection (NCT04461340) | Recruiting | 40 | July 25, 2020 | 20 patients will receive sirolimus (oral dose of 6 mg on day 1 followed by 2 mg daily for 9 days) plus national standard of care therapy against COVID 19 | Placebo plus standard medical care |
| Sirolimus treatment in hospitalised patients with COVID-19 pneumonia (NCT04341675) | Recruiting | 30 | April 24, 2020 | Sirolimus 6 mg on day 1 followed by 2 mg daily for the next 13 days or until hospital discharge, whichever happens sooner | Placebo plus standard medical care |
| Sirolimus in COVID-19 phase 1 (NCT04371640) | Recruiting | 40 | July 6, 2020 | Sirolimus 10 mg on day 1 followed by 5 mg on days 2–7 plus standard medical care | Placebo plus standard medical care |
| Hydroxychloroquine in combination with azithromycin or sirolimus for treating patients with COVID-19 (NCT04374903) | Not yet recruiting | 58 | May 1, 2020 | Participants will receive 600 mg hydroxychloroquine orally for 10 days and 250 mg azithromycin orally and daily for 10 days, or sirolimus 4 mg orally for 1 day then 2 mg orally daily for 9 days | Placebo plus standard medical care |
| Phase 3 study to determine if RTB101 reduces the severity of COVID-19 in older adults residing in nursing homes (NCT04409327) | Recruiting | 550 | July 11, 2020 | 10 mg daily RTB101 mTORC1 inhibitor (once daily for 4 weeks) | Placebo plus standard medical care |

These studies were found using a search for COVID-19-related clinical trials on ClinicalTrials.gov on Oct 23, 2020. mTOR=mechanistic target of rapamycin. mTORC1=mTOR complex 1.

***Table:*** **Clinical trials of mTOR inhibitors and treatment of COVID-19**

***Panel:*** **Initial recommendations for a clinical trial assessing the effects of rapamycin on COVID-19 outcomes and vaccine response**

**General design**
An ideal design is a double masked and placebo-controlled randomised controlled trial.

**Patient population**
We suggest enrolling older adults (eg, ≥60 years) who are predicted to have a biological age that is at least 5 years older than their chronological age.

**Cohort sizes**
Would be determined based on predicted infection rate and progression to severe outcomes. Several thousand people per study group would probably be needed.

**Dose**
5–10 mg rapamycin orally provided once per week.

**Duration**
6–10 weeks treatment with 8–10 months follow-up.

**Exclusion criteria**
Previous COVID-19 infection, immune compromised, or active infection.

**Endpoints**
Rates of COVID-19 infection, severity of outcomes (eg, hospitalisation, death), vaccine response (if available).

medications. Risk of serious complications, even from acute overdose with rapamycin, is extremely low.[75] For this reason, we believe that short-term treatment (up to a few months) with low doses (eg, a range of 5–10mg weekly) of rapamycin will have minimal adverse events and that the risk–reward ratio strongly favours the potential beneficial effects from treatment.

To our knowledge, there are no active or planned clinical trials of rapamycin or rapalogs as a preventive treatment for COVID-19. As of November, 2020, there were 214 incomplete clinical trials registered on ClinicalTrials.gov, identified using the search term "rapamycin" or "sirolimus"; five of these trials are related to COVID-19 (table). In each of the existing or planned trials, rapamycin is being tested as a treatment in hospitalised patients with confirmed COVID-19, with primary endpoints such as the change in SARS-CoV-2 viral burden and time to clinical recovery. Thus, the rationale for potential efficacy in these trials, based on the ability of rapamycin to prevent the cytokine storm seen in patients with severe COVID-19[76,77] or its potential direct anti-viral effects[78], is quite different from the effects of rapamycin on biological ageing. The biopharmaceutical company resTORbio (Boston, MA, USA) initiated a small clinical trial of RTB101 in nursing home residents, to determine whether COVID-19 severity is affected by the drug (table). The US Food and Drug Administration (FDA)-approved endpoint for this trial is "the percentage of subjects who develop laboratory-confirmed COVID-19 with protocol-defined progressive symptoms or are hospitalized or die through four weeks of study drug treatment".[79] Although there is supportive data from a phase 2 study[57] suggesting that everolimus plus RTB101 can improve immune function in older people, RTB101 acts by a different biochemical mechanism from rapamycin and has not yet been shown preclinically to have effects on biological ageing.[58] Thus, although we are hopeful that these ongoing clinical trials will prove successful, none of them address the possibility that rapamycin will rejuvenate immune function in older people and afford protection against COVID-19 to the most susceptible individuals.

We strongly advocate for a large-scale clinical trial in at-risk populations to test for prevention of COVID-19 by rapamycin. The rationale for such a trial is provided by the observed ability of rapamycin and rapalogs to reverse age-related declines in immune function in preclinical models and in people. Older patients have substantially worse clinical outcomes following COVID-19 infection, and preventive treatment with rapamycin is predicted to reduce rates of infection and improve clinical outcomes by reducing the number and severity of complications in biologically aged patients. Based on research done in mice, we hypothesise that rapamycin will restore immune function corresponding to approximately 20 years of biological age, thereby reducing severe outcomes and death from COVID-19 by approximately 4–10-times. Furthermore, enhanced immune function following rapamycin treatment is expected to improve the response to the COVID-19 vaccines and provide ongoing protection against other infections that preferentially affect older people.

The details of a well designed randomised clinical trial would need to be carefully considered, including the dose of rapamycin, duration of treatment, demographic features of the patients enrolled in the study, specific endpoints to be evaluated, the duration of follow-up, and necessary cohort sizes to reach statistical power (panel, appendix). Although the simplest study design would include only placebo and rapamycin treatment groups, a multi-arm design that is worth exploring could include additional treatment with metformin. Metformin is the most widely used anti-diabetes drug globally and is being tested for beneficial effects on ageing through the Targeting Aging with Metformin global study.[80] The preclinical evidence that metformin can positively affect the aged immune system is less robust than that for rapamycin; however, there is accumulating evidence that people with diabetes taking metformin are at reduced risk of severe outcomes or death from COVID-19 compared with people with diabetes not taking metformin.[81] Furthermore, metformin combined with rapamycin in mice is thought to improve metabolic function and slightly further increase lifespan, relative to rapamycin alone.[82]

One innovative feature that we suggest should be incorporated into a trial is the consideration of predicted biological age as an enrolment criterion. Enrolment based on chronological age is common in clinical

studies, similar to the design of the rapalog trials that investigated influenza vaccine response.[56,57] However, we propose that it could be useful to consider newly developed measures of predicted biological age for geroprotective clinical trials. Such biological age predictors could include estimates of epigenetic age using commonly applied epigenetic clocks[83] and so-called deep ageing clocks,[84] based on signatures derived from blood biochemistry, imaging, transcriptomics, and other types of available data. Patients whose biological age exceeds their chronological age by a chosen threshold (eg, 5 years) could be enrolled, thus targeting individuals at the highest risk for negative outcomes and death and who are predicted to receive the greatest benefit from a geroprotective intervention such as rapamycin. Although we recognise that the mechanisms and predictive power of current biological age estimators have yet to be clinically validated and could present unique challenges from a regulatory perspective, there is growing consensus among researchers investigating artificial intelligence and ageing that these tools can provide valuable insights into underlying physiological states that affect risk for age-related diseases and for all-cause mortality. However, they could be used as auxiliary markers until clinical validation in COVID-19 has been achieved.

A final consideration might be whether, even once shown to be efficacious, widespread use of a geroprotective intervention is economically feasible or justified, given the strain on many national health-care systems. Because there is more than one COVID-19 vaccine available, there is a danger that the incentive to continue to develop novel preventive therapies will decrease. However, influenza deaths still number in the hundreds of thousands each year even with effective vaccines, and those most susceptible to severe cases of both COVID-19 and influenza are also the least likely to mount an effective vaccine response. Thus, from the perspective of cost in terms of human lives, justification for this type of approach is obvious. It is also well established that the total economic benefit from a successful geroprotective therapy far outweighs the cost of development and implementation. Work from Goldman[85] and Olshansky[86] done before the COVID-19 pandemic has estimated that the total economic benefit from such an intervention will exceed US$7 trillion over the next 3–4 decades. The total economic value of an effective geroprotective strategy is likely to be substantially greater today than before the pandemic.

## Conclusion

SARS-CoV-2 disproportionately affects older people and people with comorbidities, with likelihood of severe complications and death mirroring that of other age-associated diseases. Inhibition of mTOR has been shown to delay or reverse many age-related phenotypes, including declining immune function. There is an urgent need for a precision medicine trial using a functional metric of ageing that investigates individuals assessed by biological age, who can then be further stratified into groups of those individuals who achieve optimal outcomes and benefit from the treatment. Rapamycin and rapamycin derivatives (rapalogs) are FDA-approved inhibitors of mTOR with broad clinical utility and well established dosing and safety profiles. Based on pre-clinical and clinical evidence, a strong case can be made for immediate large-scale clinical trials to assess whether rapamycin and other mTOR inhibitors can enhance resilience towards communicable and non-communicable diseases, prevent COVID-19 infection in those most at risk, and improve outcomes in patients with COVID-19.

### Search strategy and selection criteria

We searched for articles, reviews, and clinical trials published in English between Jan 1, 2000, and Nov 30, 2020, using online databases PubMed, National Center for Biotechnology Information, ClinicalTrials.gov, and the US National Library of Medicine. The keywords used were "COVID-19", "rapamycin", "mTOR", "ageing", "inflammation" and "geroprotection". The reference list was generated on the basis of novelty and relevance to the scope of this Personal View. COVID-19 statistics were from Worldometer.

For the **Worldometer statistics on COVID-19** see https://www.worldometers.info/coronavirus

**Contributors**

AZ came up with the concept for the Personal View. EB, RCS, and MK did the literature search. EB, RS, AZ, and MK wrote and revised the Personal View. RS had the final responsibility to submit.

**Declaration of interests**

MK served as a scientific advisor for resTORbio from 2018 to 2019. EB received a research grant from Krebsliga Schweiz (BIL KFS 4261-08-2017), outside the submitted work. RCS is the Director of Ageing Research at King's, Faculty of Life Sciences and Medicine, King's College London, funded by a King's Together grant (MKO3600). MK is the Director of and receives support from the University of Washington Nathan Shock Center of Excellence in the Basic Biology of Aging. MK has received a research grant from the National Institutes of Health. AZ is an Adjunct Professor at the Buck Institute for Research on Aging, CA, USA and CEO of Insilico Medicine and Deep Longevity, Hong Kong, China.

**Acknowledgments**

This Personal View was partly funded by a National Institutes of Health grant (P30AG013280), which was a research grant to MK.

**References**

1 Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV. Remodelling of the immune response with ageing: immunosenescence and its potential impact on COVID-19 immune response. *Front Immunol* 2020; **11:** 1748.

2 Kaeberlein M. COVID-19: why it kills the elderly and what we should do about it. May 17, 2020. https://thehill.com/opinion/healthcare/498069-covid-19-why-it-kills-the-elderly-and-what-we-should-do-about-it (accessed Nov 23, 2020).

3 Kaeberlein M. Time for a new strategy in the war on Alzheimer's disease. *Public Policy Aging Rep* 2019; **29:** 119–22.

4 Willyard C. How anti-ageing drugs could boost COVID vaccines in older people. *Nature* 2020; **586:** 352–54.

5 López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* 2013; **153:** 1194–217.

6 Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. *Cell* 2014; **159:** 709–13.

7 Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 2014; **69** (suppl 1)**:** S4–9.

8 Panda A, Arjona A, Sapey E, et al. Human innate immunosenescence: causes and consequences for immunity in old age. *Trends Immunol* 2009; **30:** 325–33.

9 Aiello A, Farzaneh F, Candore G, et al. Immunosenescence and its hallmarks: how to oppose aging strategically? A review of potential options for therapeutic intervention. *Front Immunol* 2019; **10:** 2247.

10 Barbé-Tuana F, Funchal G, Schmitz CRR, Maurmann RM, Bauer ME. The interplay between immunosenescence and age-related diseases. *Semin Immunopathol* 2020; **42:** 545–57.

11 Zhavoronkov A. Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections. *Aging (Albany NY)* 2020; **12:** 6492–510.

12 Cox LS, Bellantuono I, Lord JM, et al. Tackling immunosenescence to improve COVID-19 outcomes and vaccine response in older adults. *Lancet Healthy Longev* 2020; **1:** e55–57.

13 Walters HE, Cox LS. mTORC inhibitors as broad-spectrum therapeutics for age-related diseases. *Int J Mol Sci* 2018; **19:** e2325.

14 Johnson SC, Rabinovitch PS, Kaeberlein M. mTOR is a key modulator of ageing and age-related disease. *Nature* 2013; **493:** 338–45.

15 Kennedy BK, Lamming DW. The mechanistic target of rapamycin: the grand ConducTOR of metabolism and aging. *Cell Metab* 2016; **23:** 990–1003.

16 Pitt JN, Kaeberlein M. Why is aging conserved and what can we do about it? *PLoS Biol* 2015; **13:** e1002131.

17 Schmelzle T, Hall MN. TOR, a central controller of cell growth. *Cell* 2000; **103:** 253–62.

18 Kaeberlein M, Powers RW 3rd, Steffen KK, et al. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. *Science* 2005; **310:** 1193–96.

19 Powers RW 3rd, Kaeberlein M, Caldwell SD, Kennedy BK, Fields S. Extension of chronological life span in yeast by decreased TOR pathway signaling. *Genes Dev* 2006; **20:** 174–84.

20 Jia K, Chen D, Riddle DL. The TOR pathway interacts with the insulin signaling pathway to regulate *C elegans* larval development, metabolism and life span. *Development* 2004; **131:** 3897–906.

21 Kapahi P, Zid BM, Harper T, Koslover D, Sapin V, Benzer S. Regulation of lifespan in *Drosophila* by modulation of genes in the TOR signaling pathway. *Curr Biol* 2004; **14:** 885–90.

22 Wu JJ, Liu J, Chen EB, et al. Increased mammalian lifespan and a segmental and tissue-specific slowing of aging after genetic reduction of mTOR expression. *Cell Rep* 2013; **4:** 913–20.

23 Stanfel MN, Shamieh LS, Kaeberlein M, Kennedy BK. The TOR pathway comes of age. *Biochim Biophys Acta* 2009; **1790:** 1067–74.

24 Lamming DW, Ye L, Katajisto P, et al. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science* 2012; **335:** 1638–43.

25 Eltschinger S, Loewith R. TOR complexes and the maintenance of cellular homeostasis. *Trends Cell Biol* 2016; **26:** 148–59.

26 Saxton RA, Sabatini DM. mTOR signalling in growth, metabolism, and disease. *Cell* 2017; **168:** 960–76.

27 Martin DE, Hall MN. The expanding TOR signaling network. *Curr Opin Cell Biol* 2005; **17:** 158–66.

28 Lee MB, Carr DT, Kiflezghi MG, et al. A system to identify inhibitors of mTOR signaling using high-resolution growth analysis in *Saccharomyces cerevisiae*. *Geroscience* 2017; **39:** 419–28.

29 Robida-Stubbs S, Glover-Cutter K, Lamming DW, et al. TOR signaling and rapamycin influence longevity by regulating SKN-1/Nrf and DAF-16/FoxO. *Cell Metab* 2012; **15:** 713–24.

30 Bjedov I, Toivonen JM, Kerr F, et al. Mechanisms of life span extension by rapamycin in the fruit fly *Drosophila melanogaster*. *Cell Metab* 2010; **11:** 35–46.

31 Harrison DE, Strong R, Sharp ZD, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 2009; **460:** 392–95.

32 Anisimov VN, Zabezhinski MA, Popovich IG, et al. Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice. *Cell Cycle* 2011; **10:** 4230–36.

33 Komarova EA, Antoch MP, Novototskaya LR, et al. Rapamycin extends lifespan and delays tumorigenesis in heterozygous p53+/- mice. *Aging (Albany NY)* 2012; **4:** 709–14.

34 Wilkinson JE, Burmeister L, Brooks SV, et al. Rapamycin slows aging in mice. *Aging Cell* 2012; **11:** 675–82.

35 Livi CB, Hardman RL, Christy BA, et al. Rapamycin extends life span of Rb1+/- mice by inhibiting neuroendocrine tumors. *Aging (Albany NY)* 2013; **5:** 100–10.

36 Neff F, Flores-Dominguez D, Ryan DP, et al. Rapamycin extends murine lifespan but has limited effects on aging. *J Clin Invest* 2013; **123:** 3272–91.

37 Fok WC, Chen Y, Bokov A, et al. Mice fed rapamycin have an increase in lifespan associated with major changes in the liver transcriptome. *PLoS One* 2014; **9:** e83988.

38 Miller RA, Harrison DE, Astle CM, 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.

39 Popovich IG, Anisimov VN, Zabezhinski MA, et al. 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.

40 Bitto A, Ito TK, Pineda VV, et al. Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. *eLife* 2016; **5:** e16351.

41 Miller RA, Harrison DE, Astle CM, 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.

42 Arriola Apelo SI, Pumper CP, Baar EL, Cummings NE, Lamming DW. Intermittent administration of rapamycin extends the life span of female C57BL/6J mice. *J Gerontol A Biol Sci Med Sci* 2016; **71:** 876–81.

43 Zhang Y, Bokov A, Gelfond J, et al. Rapamycin extends life and health in C57BL/6 mice. *J Gerontol A Biol Sci Med Sci* 2014; **69:** 119–30.

44 Halloran J, Hussong SA, Burbank R, et al. Chronic inhibition of mammalian target of rapamycin by rapamycin modulates cognitive and non-cognitive components of behavior throughout lifespan in mice. *Neuroscience* 2012; **223:** 102–13.

45 Majumder S, Caccamo A, Medina DX, et al. Lifelong rapamycin administration ameliorates age-dependent cognitive deficits by reducing IL-1β and enhancing NMDA signalling. *Aging Cell* 2012; **11:** 326–35.

46 Chiao YA, Kolwicz SC, Basisty N, et al. Rapamycin transiently induces mitochondrial remodeling to reprogram energy metabolism in old hearts. *Aging (Albany NY)* 2016; **8:** 314–27.

47 Dai DF, Karunadharma PP, Chiao YA, et al. Altered proteome turnover and remodeling by short-term caloric restriction or rapamycin rejuvenate the aging heart. *Aging Cell* 2014; **13:** 529–39.

48 Flynn JM, O'Leary MN, Zambataro CA, et al. Late-life rapamycin treatment reverses age-related heart dysfunction. *Aging Cell* 2013; **12:** 851–62.

49 Chen C, Liu Y, Liu Y, Zheng P. mTOR regulation and therapeutic rejuvenation of aging haematopoietic stem cells. *Sci Signal* 2009; **2:** ra75.

50 Shavlakadze T, Zhu J, Wang S, et al. Short-term low-dose mTORC1 inhibition in aged rats counter-regulates age-related gene changes and blocks age-related kidney pathology. *J Gerontol A Biol Sci Med Sci* 2018; **73:** 845–52.

51 An JY, Kerns KA, Ouellette A, et al. Rapamycin rejuvenates oral health in aging mice. *eLife* 2020; **9:** 9.

52 An JY, Quarles EK, Mekvanich S, et al. Rapamycin treatment attenuates age-associated periodontitis in mice. *Geroscience* 2017; **39:** 457–63.

53 Yilmaz OH, Katajisto P, Lamming DW, et al. mTORC1 in the Paneth cell niche couples intestinal stem-cell function to calorie intake. *Nature* 2012; **486:** 490–95.

54 Garcia DN, Saccon TD, Pradiee J, et al. Effect of caloric restriction and rapamycin on ovarian aging in mice. *Geroscience* 2019; **41:** 395–408.

55 Kaeberlein M. mTOR Inhibition: from aging to autism and beyond. *Scientifica (Cairo)* 2013; **2013:** 849186.

56 Mannick JB, Del Giudice G, Lattanzi M, et al. mTOR inhibition improves immune function in the elderly. *Sci Transl Med* 2014; **6:** 268ra179.

57 Mannick JB, Morris M, Hockey HP, et al. TORC1 inhibition enhances immune function and reduces infections in the elderly. *Sci Transl Med* 2018; **10:** eaaq1564.

58 Kaeberlein M. RTB101 and immune function in the elderly: interpreting an unsuccessful clinical trial. *Transl Med Aging* 2020; **4:** 32–34.

59 Liu TJ, Koul D, LaFortune T, et al. NVP-BEZ235, a novel dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor, elicits multifaceted antitumor activities in human gliomas. *Mol Cancer Ther* 2009; **8:** 2204–10.

60 Liu Y, Wan WZ, Li Y, Zhou GL, Liu XG. Recent development of ATP-competitive small molecule phosphatidylinostitol-3-kinase inhibitors as anticancer agents. *Oncotarget* 2017; **8:** 7181–200.

61 Liu Q, Kang SA, Thoreen CC, et al. Development of ATP-competitive mTOR inhibitors. *Methods Mol Biol* 2012; **821:** 447–60.

62 Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. *Nat Rev Dis Primers* 2018; **4:** 3.

63 Keilich SR, Bartley JM, Haynes L. Diminished immune responses with aging predispose older adults to common and uncommon influenza complications. *Cell Immunol* 2019; **345:** 103992.

64 Kraig E, Linehan LA, Liang H, et al. A randomised 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.

65 Blagosklonny MV. Rapamycin for longevity: opinion article. *Aging (Albany NY)* 2019; 11: 8048–67.

66 Sills AM, Artavia JM, DeRosa BD, Ross CN, Salmon AB. Long-term treatment with the mTOR inhibitor rapamycin has minor effect on clinical laboratory markers in middle-aged marmosets. *Am J Primatol* 2019; **81:** e22927.

67 Urfer SR, Kaeberlein TL, Mailheau S, et al. A randomised controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs. *Geroscience* 2017; **39:** 117–27.

68 Urfer SR, Kaeberlein TL, Mailheau S, et al. Asymptomatic heart valve dysfunction in healthy middle-aged companion dogs and its implications for cardiac aging. *Geroscience* 2017; **39:** 43–50.

69 Global Burden of Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018; **18:** 1191–210.

70 DeJong EN, Surette MG, Bowdish DME. The gut microbiota and unhealthy aging: disentangling cause from consequence. *Cell Host Microbe* 2020; **28:** 180–89.

71 Steelman LS, Martelli AM, Cocco L, et al. The therapeutic potential of mTOR inhibitors in breast cancer. *Br J Clin Pharmacol* 2016; **82:** 1189–212.

72 Santulli G, Totary-Jain H. Tailoring mTOR-based therapy: molecular evidence and clinical challenges. *Pharmacogenomics* 2013; **14:** 1517–26.

73 Woillard JB, Kamar N, Rousseau A, Rostaing L, Marquet P, Picard N. Association of sirolimus adverse effects with m-TOR, p70S6K or raptor polymorphisms in kidney transplant recipients. *Pharmacogenet Genomics* 2012; **22:** 725–32.

74 Zaza G, Tomei P, Ria P, Granata S, Boschiero L, Lupo A. Systemic and nonrenal adverse effects occurring in renal transplant patients treated with mTOR inhibitors. *Clin Dev Immunol* 2013; **2013:** 403280.

75 Ceschi A, Heistermann E, Gros S, et al. Acute sirolimus overdose: a multicenter case series. *PLoS One* 2015; **10:** e0128033.

76 Omarjee L, Janin A, Perrot F, Laviolle B, Meilhac O, Mahe G. Targeting T-cell senescence and cytokine storm with rapamycin to prevent severe progression in COVID-19. *Clin Immunol* 2020; **216:** 108464.

77 Zheng Y, Li R, Liu S. Immunoregulation with mTOR inhibitors to prevent COVID-19 severity: a novel intervention strategy beyond vaccines and specific antiviral medicines. *J Med Virol* 2020; **92:** 1495–500.

78 Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583:** 459–68.

79 resTORbio. resTORbio announces initiation of study to evaluate if antiviral prophylaxis with RTB101 reduces the severity of COVID-19 in nursing home residents. May 28, 2020. https://ir.restorbio.com/news-releases/news-release-details/restorbio-announces-initiation-study-evaluate-if-antiviral (accessed Nov 23, 2020).

80 Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. *Cell Metab* 2016; **23:** 1060–65.

81 Hariyanto TI, Kurniawan A. Metformin use is associated with reduced mortality rate from coronavirus disease 2019 (COVID-19) infection. *Obes Med* 2020; **19:** 100290.

82 Strong R, Miller RA, Antebi A, et al. Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an α-glucosidase inhibitor or a Nrf2-inducer. *Aging Cell* 2016; **15:** 872–84.

83 Field AE, Robertson NA, Wang T, Havas A, Ideker T, Adams PD. DNA methylation clocks in aging: categories, causes, and consequences. *Mol Cell* 2018; **71:** 882–95.

84 Zhavoronkov A, Mamoshina P. Deep aging clocks: the emergence of AI-based biomarkers of aging and longevity. *Trends Pharmacol Sci* 2019; **40:** 546–49.

85 Goldman D. The economic promise of delayed aging. *Cold Spring Harb Perspect Med* 2015; **6:** a025072.

86 Olshansky SJ. Articulating the case for the longevity dividend. *Cold Spring Harb Perspect Med* 2016; **6:** a025940.