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REFERENCES

1. Need a Coronavirus Test? Being rich and famous may help. https://www.nytimes.com/2020/03/18/us/coronavirus-testing-elite.html. Accessed April 7, 2020.
2. VIPs go to the head of the line for coronavirus testing. https://www.washingtonpost.com/health/2020/03/19/nba-players-celebrities-coronavirus-test-access/. Accessed April 7, 2020.
3. White house to give coronavirus test to people 'in close proximity' to Trump, Pence. https://www.npr.org/sections/coronavirus-live-updates/2020/04/03/826853164/white-house-to-give-coronavirus-test-to-people-in-close-proximity-to-trump-pence. Accessed April 7, 2020.
4. As coronavirus deepens inequality, inequality worsens its spread. https://www.nytimes.com/2020/03/15/world/europe/coronavirus-inequality.html. Accessed April 7, 2020.
5. Coronavirus may disproportionately hurt the poor—and that's bad for everyone. https://time.com/5800930/how-coronavirus-will-hurt-the-poor/. Accessed April 7, 2020.

GEROSCIENCE AND THE CORONAVIRUS PANDEMIC: THE WHACK-A-MOLE APPROACH IS NOT ENOUGH

To the Editor: We are in the midst of a pandemic, and it is becoming increasingly clear that health systems around the world are either not adequate or stretched to the limit. The main strain comes from severely affected patients needing intensive care, ventilators, and other medical equipment currently in short supply. Although the virus has the ability to infect people of all ages and socioeconomic status, severe symptoms and mortality occur primarily in frail older adults, and they represent most of the patients overloading the hospitals.

Because those most affected are the frail older adults, I propose to add geroscience as a new tool to our strategy against COVID-19. There is no doubt that a long-term approach to this crisis involves the rapid development of vaccines and other prophylactics. But unfortunately, this takes time, and in the meantime the frail are dying. Geroscience posits that all diseases affecting primarily older adults, even diseases as disparate as cancer and heart disease, have as a common (and major) cause the declining function and resilience that often accompanies the aging process.[1] This is true for chronic diseases, but it is also true for acute ones such as COVID-19. Weakened resilience lowers our capacity to respond to the physiologic challenge of an acute infection. Importantly, preclinical work is already showing that interventions addressing the basic biology of aging, such as elimination of senescent cells[2] or inhibition of nutrient-sensing mechanisms,[3] can have a positive effect on the ability of a variety of preclinical models to withstand both chronic and acute challenges. Some are already being tried in the clinic, and it is imperative that these approaches be further advanced rapidly.

For example, we should be testing the ability of senolytics (drugs that preferentially kill senescent cells) as a way to mitigate the cytokine storm that is widely believed to be at the core of why frail older adults are more susceptible to serious outcomes including death. Senescent cells accumulate in people as a consequence of age and disease, and they secrete multiple cytokines (the so-called senescent-associated secretory phenotype [SASP])[4] that cause inflammation, activating resident macrophages and other elements of the innate immune response. As a result, when a virus or other acute insult activates this already alert innate immune system, a deadly cytokine storm might occur. Preliminary data in mice and other models indicate that killing senescent cells with these senolytic drugs alleviates the problem.[2] This needs to be tested immediately in animal models challenged with COVID-19, and shortly, in controlled clinical trials in patients. It is important to emphasize that senolytics do not directly target the mechanism of pathogenesis of this (or any other) virus, or even the immune system. They target the aging process itself. However, it is possible that attenuating the nonspecific cytokine storm exacerbated in frail older adults affords time for the patient to develop a better and stronger antigen-specific immune response to COVID-19 or other pathogens.

Other geroscience approaches currently under consideration include inhibition of the mechanistic target of rapamycin (mTOR) pathway of nutrient sensing.[3] Inhibition of this pathway with a combination of everolimus (a derivative of rapamycin) and RTB101 (a catalytic site mTOR inhibitor), was shown to be effective in increasing antibody titers against influenza vaccination.[5] In phase 2 trials in adults 65 years of age and older, RTB101 upregulated pan-antiviral gene expression, decreased the levels of inflammatory cytokines, and decreased the incidence and severity of laboratory-confirmed viral respiratory tract infections including coronavirus infections. Although a recent large phase 3 trial of RTB101 failed to reach its primary end point, that point was not the incidence or severity of viral respiratory tract infections. Importantly, both everolimus and RTB101 have been shown to be well tolerated in older adults at the doses and frequency used in these studies. Again, the approach here is not either to attack this specific virus or to boost the immune system by specific targeting; rather, the approach is to improve health including immune health by targeting one of the main pillars of aging biology.

Of note, this geroscience approach is not specific to COVID-19, but once tried and proven, it would be effective against any future pandemics or epidemics. As a note of caution, senolytics and other geroscience-based approaches would not limit infection rates. They would only protect the frail against the more severe consequences of the disease including death. Thus the geroscience approach needs to be viewed as an adjuvant to the current approaches, not a replacement.

COVID-19 is the largest pandemic in decades, but it is not unusual. We have been there before with severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), as well as the seasonal flu. In each case, a large mobilization of research and health resources resulted in

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effective treatments and/or prophylactics including vaccines. This is an appropriate response, but it is not sufficient. In the long run, we will succeed in our efforts against COVID-19, but in a few years we will be confronted with a new challenge, in the form of another virus that has succeeded in zoonotic transmission, and the cycle will begin again. Of note, the geroscience approach is not "ageist": the affected individuals are not those "chronically old," but rather those that are "physiologically old" through loss of function and resilience, irrespective of their chronological age.

Viewed more globally, the problem is that our approach to medicine is reactive rather than proactive and focused on diseases rather than improvement of health and resilience. As a general approach, modern medicine focuses on developing treatments against chronic diseases such as cardiovascular or cancer or diabetes, to try to redress damage already produced, and there is a relatively scarce effort at improving the individual's ability to fight those diseases, other than through diet and exercise.

In the case of COVID-19, the frail older adults are the most affected, in part because they often already present with multiple morbidities, in the form of more than one chronic disease. And then the complications get exacerbated by the sudden appearance of yet one more disease: acute infections with SARS-CoV2. In such patients, addressing any of their comorbidities (including COVID-19) amounts to playing a game of whack-a-mole. You take care of disease 1, only for disease 2 to become the major issue. This is not the case with geroscience, which is disease blind, in that it aims to improve the host's defenses, irrespective of the challenge at hand, so the same strategy can be rapidly deployed in future epidemics.

Because the immediate problem at hand is a virus attacking mainly the respiratory tract, naturally the focus has been on the immune system and the lungs. We need to continue those efforts to reduce the incidence and severity of the pandemic. But protecting the more vulnerable among us will require a different approach. Here I have proposed a more general strategy that should serve us to fight not only the current COVID-19 epidemic, but also all those that are yet to come. We have been successful in fighting pandemics and epidemics in the past, and no doubt we will continue to be successful. However, the current approach of addressing each onslaught as it occurs does not seem to be a particularly effective strategy. Geroscience is a better solution.

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REFERENCES

1. Sierra F, Kohanski R. Geroscience offers a new model for investigating the links between aging biology and susceptibility to aging-related chronic diseases. Public Policy Aging Rep. 2013;23:7-11.
2. Yousefzadeh MJ, Zhu Y, McGowan SJ, et al. Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine. 2018;36:18-28.
3. Johnson SC, Rabinovich PS, Kaeberlein M. mTOR is a key modulator of ageing and age-related disease. Nature. 2013;493:338-345.
4. Coppé J-P, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008;6:2853-2868.
5. Mannick JB, Morris M, Hockey H-UP, et al. TORC1 inhibition enhances immune function and reduces infections in the elderly. Science Transl Med. 2018;10(449):eaaq1564.