Tackling immunosenescence to improve COVID-19 outcomes and vaccine response in older adults

The COVID-19 pandemic serves as a potent reminder that older people are at very high risk of adverse outcomes from infectious disease because of comorbidities associated with ageing and decreased immunological competence (immunosenescence). Care home residents are particularly at risk because physiological vulnerability is compounded by cohabitation with other frail adults, increasing exposure and risk of infection. Immunosenescence not only increases susceptibility to disease but also blunts the effectiveness of vaccines[1]—one of our most powerful tools for preventing infections—with annual influenza vaccinations only 30–40% effective in the most at-risk older populations. In the race for creating a vaccine against COVID-19, immunosenescence is most likely to present a disincentive to the inclusion of older people in trials, and vaccine formulations effective in younger people (<65 years) might not engender immunity in older populations. Finding ways to alleviate immunosenescence is a priority to improve the health of ageing populations, but to do so requires a robust understanding of the underlying causes of age-related decline and immunosenescence.

Biological ageing results in loss of physiological reserve—the capacity of a cell, tissue, or organ system to function beyond its basal level in response to increases in physiological demands. This loss of reserve is now known to be underpinned by a discrete set of biological mechanisms that can be therapeutically targeted. One such mechanism is cellular senescence, leading to the accumulation of dysfunctional cells that secrete tissue-degrading proteases plus pro-inflammatory cytokines and chemokines, causing local and systemic harm. Senescence of immune cells (eg, via proliferative exhaustion), combined with depletion of naive T cells through thymic atrophy, exacerbates age-related loss of immunity to novel pathogens and vaccines. Approaches aimed at restoring immune function and improving tissue and organ physiology are thus likely to be important in mitigating the catastrophic effect of infections on older people.

Geroprotectors are drugs that target core biological mechanisms underlying ageing[2,3] and are able to counteract the loss of function occurring with age in multiple organ systems, including the immune system.

	Molecular target	FDA-approved indication	Effect on senescence or immunosenescence
mTOR inhibitors: first generation (allosteric, non-competitive)—sirolimus and everolimus; second generation (active site inhibitors, competitive with ATP)—RTB101 and AZD8055	First generation inhibitors target mTORC1, decrease translation, increase autophagy and alter metabolism; second generation inhibitors target mTORC1 and possibly mTORC2, as above and also affect cytoskeleton	Cancer; immunosuppressant in kidney transplant rejection and some autoimmune conditions (NB doses for these indications are far higher than those that provide geroprotection)	Improve outcomes in many age-related diseases;[4] improve response to flu vaccination[5] (ACTRN12613001351707); decrease incidence and severity of respiratory tract infections in older adults;[6] sirolimus in trials (NCT04341675) for COVID-19 pneumonia; RTB101 in trials for COVID-19 prophylaxis in older people in the community (NCT04584710) or in nursing homes (NCT04409327), geroprotective at 1/120th maximum tolerated dose, well tolerated in older adults
Statins	Pleiotropic: main target is the HMG-CoA reductase pathway; might also target small G protein Rho, affecting the actin cytoskeleton and cell motility	Reduction of low density lipoprotein cholesterol	Increase neutrophil cytokinesis and NETosis; decrease sepsis, organ failure and death in older adults hospitalised with community acquired pneumonia[7] (EudraCT 2012-00343-29); currently in many trials for COVID-19 (NCT04407273, NCT04390074, NCT04348695, NCT04426084, NCT04333407, NCT04380402, and NCT04343001) and reported to COVID-19 deaths[8]
Dasatinib (in combination with plant flavonoid quercetin)	src-family tyrosine kinase inhibitor (also inhibits BCR-ABL kinase)	Cancer	Senolytic—ie, selectively kill senescent cells; improve physiological function in idiopathic pulmonary fibrosis;[9] in phase 2 trials in chronic kidney disease (NCT02848131)
Metformin	Pleiotropic: main target is mitochondrial complex I, inhibition of which leads to activation of AMPK, and inhibition of acetyl CoA carboxylase; increases GLP-1 in gut	Type 2 diabetes	Immunomodulatory especially through T helper cell balance, leading to reduced autoantibodies, cytokines, and neutrophil NETosis; retrospective analysis suggests might improve outcomes for female patients with obesity and diabetes who have COVID-19[10]

Table: **Examples of geroprotective agents**

These drugs might offer unique opportunities to protect vulnerable older people from infectious pathogens and might help to mitigate the consequences of acute infections and chronic multimorbidity, for example by acting to alleviate detrimental effects of senescent cells. Several drugs have shown geroprotective efficacy in preclinical testing, with several agents repurposed (often at very low doses) from existing alternative clinical indications (table). Of particular note for reversal of immunosenescence is that short-term treatment with geroprotective mTOR inhibitors (everolimus and BEZ235–RTB101 [Basel, Switzerland]) was found to improve responses to influenza vaccination in older adults, with benefits possibly persisting for a year after treatment.[5] Such drugs suppress excess senescence-associated inflammation while also improving innate immunity. RTB101 has been shown to upregulate interferon-induced antiviral gene expression in older adults,[6] which is the first line of immune defence against viral infections such as COVID-19. Trials of RTB101 and other mTOR inhibitors to prevent and treat COVID-19 are ongoing (table). Similarly, statins can act as geroprotectors to support immunity, positively affecting innate and adaptive immune responses to improve pneumonia outcomes in older adults.[7] Statins are also now being tested for benefit in COVID-19 (table).[8]

Given such promise, what needs to happen now to make progress towards widespread clinical use of geroprotectors? The majority of current experimental drug trials—both for COVID-19 and for non-COVID infections—do not include older adults with multimorbidity. This exclusion of older people from trials must change if we are to understand the efficacy of new drugs in this population group who are at the highest risk. Additionally, randomised controlled trials of geroprotectors are needed, both as adjuvant therapy to enhance vaccine responses and to improve immunity in older people at risk of contracting COVID-19 and other infections. Care home residents, too often neglected during the COVID-19 pandemic, have much to gain from such an approach and should be prioritised for involvement in geroprotective trials. Candidate medications are already widely used in the clinic and have good safety profiles, especially at the low doses needed for geroprotection. Notably, short-term treatment can give long-term protection, as seen with drugs that remove senescent cells (senolytics)[9] that have a hit-and-run activity requiring only infrequent administration thus maximising benefit while minimising side-effects. Finally, we need regulatory bodies to support applications for appropriate clinical testing of geroprotectors, and to provide appropriate frameworks for their marketing authorisation and regulatory approval. The promise of geroprotective drugs will, if realised, extend far beyond the COVID-19 pandemic to improve overall health resilience in our ageing populations. Now is the time to test them.

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