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Title	**Senolytic therapy alleviates physiological human brain aging and COVID-19 neuropathology**
Abstract (max 300w)	Aging is the primary risk factor for most neurodegenerative diseases, and recently coronavirus disease 2019 (COVID-19) has been associated with severe neurological manifestations that can eventually impact neurodegenerative conditions in the long-term. The progressive accumulation of senescent cells in vivo strongly contributes to brain aging and neurodegenerative co-morbidities but the impact of virus-induced senescence in the aetiology of neuropathologies is unknown. Here, we show that senescent cells accumulate in physiologically aged brain organoids of human origin and that senolytic treatment reduces inflammation and cellular senescence; for which we found that combined treatment with the senolytic drugs dasatinib and quercetin rejuvenates transcriptomic human brain aging clocks. We further interrogated brain frontal cortex regions in postmortem patients who succumbed to severe COVID-19 and observed increased accumulation of senescent cells as compared to age-matched control brains from non-COVID-affected individuals. Moreover, we show that exposure of human brain organoids to SARS-CoV-2 evoked cellular senescence, and that spatial transcriptomic sequencing of virus-induced senescent cells identified a unique SARS-CoV-2 variant-specific inflammatory signature that is different from endogenous naturally-emerging senescent cells. Importantly, following SARS-CoV-2 infection of human brain organoids, treatment with senolytics blocked viral retention and prevented the emergence of senescent corticothalamic and GABAergic neurons. Furthermore, we demonstrate in human ACE2 overexpressing mice that senolytic treatment ameliorates COVID-19 brain pathology following infection with SARS-CoV-2. In vivo treatment with senolytics improved SARS-CoV-2 clinical phenotype and survival, alleviated brain senescence and reactive astrogliosis, promoted survival of dopaminergic neurons, and reduced viral and senescence-associated secretory phenotype gene expression in the brain. Collectively, our findings demonstrate SARS-CoV-2 can trigger cellular senescence in the brain, and that senolytic therapy mitigates senescence-driven brain aging and multiple neuropathological sequelae caused by neurotropic viruses, including SARS-CoV-2.

Abstract deadline: Jan 20 (Please send to cjcadradmin@qbi.uq.edu.au)