

With the ~~Recent~~ advancements in ~~the field of~~ translational geroscience, ~~it has have~~ ~~become~~ made it possible to better disentangle the intricacies of biological ~~phenomenon~~ phenomena underlying healthy aging and age-related diseases in humans (Sierra, 2016). Accumulated evidence ~~have has~~ proposed that the decline of fitness ~~decline~~ in mammals ~~are~~ results from the functional interconnections between the nine hallmarks of aging, ~~that which~~ can be further subdivided into three categories, namely, primary hallmarks (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis); ~~);~~ antagonistic hallmarks (deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence); ~~);~~ and integrative hallmarks (stem cell exhaustion, and altered intercellular communication) (Carlos López-Otín et al., 2013). Although the current mechanistic findings in these categories may not thoroughly define aging, ameliorating any ~~one or more~~ of these hallmarks could potentially impact ~~the overall~~ healthspan.

Aging is a malleable process in general. In contrast to disease-specific approaches, geroscience-oriented approaches have the capacity to prevent multiple age-related diseases simultaneously, ~~and~~ thereby promoting healthy aging, and delaying the onset of dependency and disability (Kaeberlein, 2017). ~~Indeed, s~~ Several geroprotective interventional studies ~~targeting the~~ that target the hallmarks of aging have been demonstrated to have highly translational potential. Generally, mTOR ~~mTOR~~ inhibits autophagy and promotes protein synthesis, which may lead to mitochondrial dysfunction and ~~induces~~ stem cell exhaustion (Stallone et al., 2019). These mTOR activation events ultimately promote tissue dysfunction, ~~and thus~~ accelerate ~~accelerating~~ the pathogenesis of various aging diseases. Meanwhile, rapamycin, ~~an~~ FDA-approved mTOR inhibitor, is not only capable of extending healthspan, but also mitigating ~~mitigates any~~ undesirable immune functions relevant to aging and inflammation (Johnson et al., 2013; ~~;~~ Hurez et al., 2015). Metformin, a first-line used-applied for ~~the~~ treatment of type 2 diabetes (T2D), has also been shown

to prolong lifespan, and slow down the onset of age-related disease. *Caenorhabditis elegans* is a powerful model system in behavioral and molecular aging research, primarily due to the presence of lifespan-regulating genes associated with metabolic pathways, short lifespan and clear physiological changes ~~as they age~~ (Gao et al., 2018; Son et al., 2019). Molecular mechanistic studies have shown that metformin ~~inhibited~~ inhibits TORC1 and ~~activated~~ activates AMPK through the v-ATPase-regulator lysosomal pathway, ~~and thereby~~ leading to the extension of lifespan in *C. elegans* (Chen et al., 2017). Thirty-week metformin-supplemented dietary treatment at the middle age period also improved physical performance, insulin sensitivity and lipid profile, ~~as well as and reducing~~ reduced oxidative stress- and chronic inflammatory markers; ~~which that~~ promote health aging in male C57BL/6 mice (Martin-Montalvo et al., 2013). Despite these drugs being associated with promising geroprotective properties, the chronic use of rapamycin and metformin has the potential to cause metabolic impairment and gastrointestinal complications, respectively; which may further preclude their deployment as anti-aging alternatives in older adults (Schlender et al., ~~2017~~; Salmon, 2015).