# Geroprotection: A promising future

Geroprotection or anti-ageing is an important, yet poorly comprehended aspect of mid-life health. Since antiquity, medicine has betrothed itself in finding cures for its various diseases and disorders. The final aim of treating all afflictions, whether acute or chronic, in childhood or adulthood, medical or surgical, is to improve the quality of life and lifespan of the concerned individual. Ancient Indian as well as medieval European literature reflects the interest in finding anti-ageing drugs.[1] Modern literature has proposed the use of various hormones, including growth hormone, estrogen, dehydroandrosterone sulphate, and testosterone, as "elixirs" or fountains of youth.[2-4]

Recent advances in physiology have refocused attention on the science of anti-ageing. Current promising interventions for geroprotection are related to seemingly diverse fields such as medical nutrition, nutraceuticals, endocrinology and transplant medicine. However, these promising treatment modalities, whether pharmacological or not, have much in common.

Ageing is an inevitable part in life of all organisms, as essential as birth and death. Life itself can be defined as ageing.[5] The process of ageing is seen across all species, from bacteria such as *E. coli*, to yeast, nematodes, flies and mammals. In small bacteria and yeast, protein aggregates accumulate or polarize in the old pole of new cells. This asymmetrical partitioning, maintains reproductive ability of the younger cells. In insects, older members perform more dangerous activities, which may potentially expose them to life-threatening situations. Younger insects that are reproductively active yet have relatively safer duties to perform. This age-dependent division of labor, also termed as temporal polytheism, preserves youth and reproductive capacity.

The mechanism of ageing is highly conserved throughout the animal kingdom. Various biochemical and physiological processes which are implicated in the phenomenon of ageing include Insulin like Growth factor (IGF)-1 signaling free radicals or reactive oxygen species, senescence-promoting genes, Sirtuin (SIR) 2 (also known as SIRT 1), Forkhead Box – O (FOXO) transcription factors, and heat shock protein.[6] While SIR 2 and FOXO factors exhibit significant inter-species variability, a kinase enzyme known as the target of rapamycin (TOR) (mammalian TOR in mammals) is highly conserved. There are two TOR proteins or complexes: deletion of TOR 1 in yeast extends life, while deletion of TOR 2 is incompatible with life.[7]

In humans, the processes of ageing herald in midlife and are characterized by the appearance of various age-related diseases, including diabetes, cancer, neurodegeneration and cardiovascular disease.[8] It stands to reason; therefore, that a potential "cure" for ageing will be linked to therapy for some of the age-related diseases. Most interest is centered around insulin and IGF-1 pathway, because TOR causes insulin resistance via Signaling Encryption Key (SEK) signaling, while TOR inhibition is associated with insulin sensitivity and extreme longevity.[9]

The average human life span has increased noticeably. The average life expectancy has now risen to 89.6 years in Monaco and 84.43 in Macau.[10] A similar trend is seen in India, where the average citizen can now expect to live up to 64.9 years (year 2009), a great improvement on the 42.4 years reported in 1960.[11] These gains in human life expectancy have largely been fuelled by a reduction in infant and childhood mortality rates, and by public health interventions such as better nutrition and sanitation. For further improvement in the human life span, however, we shall have to focus on geriatric health.

Medical anthropologists and other researchers have studied a few ethnic groups, which are famed for their longevity. The Okinawans, who inhabit the Okinawa islands of Japan, are long-lived people who attribute their health to eating less. They follow a culture of "*hara hachi bu*," which means eating only till one in 80% full.[12] The concept is "Eat until you are eight parts (out of ten) full" or "belly 80% full." The Ashkenazi Jews, another community known for their long lifespans, have been found to have IGF-1 receptor gene mutation, associated with reduced IGF 1 response.[13] A few individuals with long lives have also been studied. Dr. Rita Levi–Mantalcini, who turned 103 in 2012, and is the oldest living Nobel Prize laureate, reportedly takes the nerve growth factor (which she discovered) in the form of eye drops, and attributes her long life to this.[14]

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## CALORIE RESTRICTION

One intervention, which has been shown to prolong lifespan by 30-50% in species ranging from roundworms to primates, is calorie restriction (CR). It is necessary, of course, to ensure that malnutrition does not occur.[15,16] CR delays the onset of age-related diseases, enhances resistance to stress, and slows functional decline in animal models. Similar effects have also been reported in human beings.[17] It works by inhibiting the nutrient–sensing TOR pathway, inducing sirtuins, reducing free radical formation, and increasing insulin sensitivity.[6] While CR may be the best intervention at present for anti-ageing, its Spartan nature may not appeal to the vast majority of population, especially in the current hedonistic era. To overcome this, work has headed on the identification and development of various calories restriction mimetics (CRMs). Research has focused on molecules that inhibit IGF-l and activate SIR 2 or SIR 1, a sirtuin family of $NAD^+$ dependent deacetylases. One such CRM, used for other indications as well, is metformin. Metformin is a biguanide, and is currently considered the line of first treatment in diabetes management.[18] This drug also acts as a CRM, as it tries to conserve energy by reducing hepatic gluconeogenesis, while promoting glucose uptake in peripheral tissues and fatty acid oxidation. Metformin has seemed to reduce the incidence of cancer, which is an age-related disease. In prospective trials, metformin use has been associated with increased survival in people with diabetes. The proposed geroprotective mechanism of metformin may overlap with and be confounded by its anti-hyperglycemic effect. The drug is thought to, both directly and indirectly, activate the enzyme AMP-activated protein kinase (AMPK), an 'energy stat' which conserves energy. Metformin has also been shown to inhibit the serine threonine kinase known as mammalian TOR, via rag GTPase, an independent of AMPK. This seems to be a more promising target for the geroprotective effects of metformin.[5,6,15]

Another CRM is reservatrol (RSV), a polyphenol nutraceutical found in red wine. It has been shown to extend the life span of *Sacchromyces cerevisae, Caenorhabditis elegans* and Drosophila melanogaster, by 18-56%. However, some researchers have reported conflicting results. In obese mice given a high-calorie diet, RSV can reverse various negative effects including impaired glucose tolerance, insulin resistance, dyslipidemia and cardiovascular dysfunction. This helps the obese mice increase their survival span. RSV has also been proven to improve health of mice fed a standard diet. It slows age-related organ and functional decline, without causing weight loss. This is achieved by mimicking the effect of CR, and also by a mechanism independent of obesity. Potential substrates of RSV include the sirtuins (SIRT1 in mammals).[5,15] Evidence is available regarding the geroprotective effects of RSV, a constituent of red wine, in humans. In fact, the term "red-wine endocrinology' has been coined to describe the various hormonal and metabolic effects of this nutraceutical.[19]

Rapamycin is another drug, with clearly delineated effects on lifespan, and well-understood target molecules. This molecule has been shown to have geroprotective effects in yeast, roundworms and flies.[6,15] In mice, a similar effect has been shown even when treatment was begun at an age corresponding to roughly 60 years in humans.[20] Rapamycin, too, is a CRM. It acts at m TOR, which is a nutrient-sensing protein that modulates the response to starvation. Similar to CR, Rapamycin inhibits TOR, by AMPK dependent and independent mechanisms, to inhibit translation and activate autophagy. This leads to extension of life span. Rapamycin is specific form TORC1, and has no effect on TORC2.[6,15] In clinical practice, Rapamycin is used as an immunosuppressant and on co-suppressive agent. Its use prevents new tumor formation and leads to regression of already existing tumors. It reduces progression of atherosclerosis, but causes hyperlipidemia.[6]

Antioxidants were earlier thought to have a beneficial effect on age-related diseases. However, most clinical trials have concluded the opposite.[21] Perhaps newer, more potent antioxidants with a geroprotective effect needs to be designed. It is also possible that combinations of antioxidants be used with TOR inhibitors in future.

Geroprotection, or anti-aging is an interesting and important yet poorly understood aspect of mid-life health. Much remains to be discovered about the physiology of ageing. While CR can certainly be purposed as a means of increasing life span in humans, one should understand the attendant risk of malnutrition, and limitation with regards to patient acceptance. While currently available animal data is robust, there is no human clinical data to support the primary prevention of death with geroprotective agents. Clinical trials are warranted in this direction. There is, however, hope for our brighter and longer future. Geroprotection has a promising future!

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