[Frontiers in Bioscience, Landmark, 26, 97-162, Jan 1, 2021]

From genoprotection to rejuvenation

Siamak Tabibzadeh[1]

Frontiers in Bioscience Research Institute in Aging and Cancer, 16471 Scientific Way, Irvine, CA 92618, USA

TABLE OF CONTENTS

1. ABSTRACT

Aging results from aberrations in signaling mechanisms and decline in biologic activities and cellular functions. Anti-aging strategies include a number of dietary, genetic, and pharmacological interventions that converge on a core network of nutrient sensors including AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), the insulin/insulin-like IIGF) growth factor signaling pathway (IIS), sirtuins, NFκB, and FOXO. Aging can be delayed and life-span and health-span can be extended by calorie and dietary restrictions, administration of NAM, NMN, NR, NAD$^+$, and by antioxidants including hydrogen sulfide. Additional measures for the age related decline in tissue homeostasis include senotherapeutics, senolytics, senomorphics, anti-inflammaging strategies, reactivation of telomerase and prevention of stem cell exhaustion. There is also a possibility to erase the signs of aging and even to reverse aging by epigenetic reprogramming and other emerging measures.

2. GENOPTORECTION STRATEGIES

Chronological aging is caused by aberrations of diverse transcriptional programs and cell signaling pathways which alter the tissue and organ functions during aging. It has been shown that a number of environmental and nutritional changes including dietary, calorie, and protein restriction can delay the inevitable consequences of aging and that life might be extended in experimental animals including *Drosophila melanogaster*, *Caenorhabditis elegans* (*C. elegans*), to mice and even in humans (1-4). Moreover, alterations of signaling pathways that deteriorate by aging have been shown to be

restored by introduction of genetic changes in yeast, flies and worms (5-6).

2.1. Calorie and dietary restriction and interventions

Some of the effects of calorie restriction (CR), AMPK and calcineurin appear to be due to the blocking of CRTC–CREB pathway (7). A complete removal of food has been shown to extend life-span in *C. elegans* (8-9). The beneficial impact of dietary restriction (DR) can be achieved by reducing nutrients, or by reducing total protein or the essential amino acids (EAA), or merely by reducing the sulfur amino acids (SAA) in the diet. It is thought that the amino acid sensors, GCN2 and mTOR, are involved in the beneficial effects of restriction of protein or selective amino acids in life extension (10). The effects of CR on longevity also seems to be attributable to the restriction of proteins or specific amino acids (11). For example, the restriction of the amino acids serine, threonine and valine, in yeast promotes stress resistance and longevity (12). As compared with glucose restriction, withdrawal of protein from the diet had a much greater effect on life-span in *Drosophila melanoganster* (13). Restricting tryptophan also appears to increase longevity in rats (14-15). Five fold reduction of L-methionine in the diet was associated with lower levels of IGF-1, insulin and glucose and a higher resistance to liver injury, and an increase in the life-span by 30% in male rats (16-17).

The extremely high life expectancy in centenarians in Okinawa, Japan may well be due to 17% lower average daily food intake of a diet, that is low in proteins and rich in vegetables, fruits and fish as well as consumption of foods which are rich in monounsaturated and polyunsaturated fatty acids (18-19). Mediterranean diet, which is rich in monounsaturated and polyunsaturated fatty acids, and is considered to promote longer telomeres, and healthy aging, reduces mortality from cerebrovascular accident (CVD) (11, 20-23). Consistent with these findings, higher intake of n-3 polyunsaturated fatty acids supports lower cognitive decline and a better cognitive performance in individuals who are on Okinawan or Mediterranean diets (24-25). CR has been shown to lower core body temperature, to reduce total and visceral fat, to improve the glucose tolerance, insulin action, adipokine, adiponectin, leptin, inflammation and interleukins, to decrease energy expenditure and loss of muscle mass and strength and to extend life-span in different model organisms (26-30). Classic CR regimens in rodents involves restriction of total food intake by 20–60%, by reducing the overall calorie intake (calorie restriction), or by intermittent or every-other-day fasting. CR attenuated the age-related increase in oxidative stress and decline in autophagy in rat skeletal muscle and induced a lower decline in insulin sensitivity in the rat liver (31-32). Intermittent fasting also improved regulation of glucose homeostasis and led to a 40% reduction in the IGF-1 levels (33-35). At least 60% of the CR group animals had less age related damage and lived longer than those that were fed *ad libitum* (36). Such diets offer overlapping functional benefits on stress resistance, metabolic fitness and life-span (37-39). There is substantial evidence that metabolism and aging are linked and that adoption of less active metabolism can prolong life for an extended period of time. One idea that arose over 70 years ago by McCay in studying rats subjected to CR, is that the decline in the supply of the food, evokes stress-resistance programs, and delays or suspends reproduction until such time that the environmental factors change and food supply is restored. These results have been repeatedly confirmed (40-44). Studies in model organisms including *C. elegans*, mice and non-human primates have repeatedly shown that CR is a promising tool in fight against aging and age related pathologies (45). In non-human primates, 30% CR led to lower incidence of age-related diseases, less loss of grey matter and improved survival, yet, these findings are at odds with a study carried out at the National Institute of Aging (NIA) study on rhesus monkeys (46-47).

CR and DR, reproducibly extend the maximum life-span in mammals, likely, by activating a biological defense response that helps organisms to survive in case of environmental adversity (48). For example, yeasts can live longer in mildly stressful conditions such as low nutrients, osmotic stress, high temperature and high salt (49-51). Together, the engagement of such defense systems have shown to extend the life-span of yeast, flies, nematodes, and

rodents (2, 52-57). In primates including humans, CR has been associated with a significant improvement in physiological functions including fasting insulin level and 24-hour energy expenditure (53,58-62). Experiments in short lived organisms such as nematodes and flies have revealed that the calorie restriction works by modifying the insulin signaling, nutrient sensing and chromosome remodeling and engages the systems that are directed at damage response pathways (5). Oxidative stress leads to a significant age dependent increase in 8-oxo-2-deoxyguanosine (oxo^{8}dG) levels in nuclear DNA (nDNA) in all tissues and increase oxo^{8}dG in mitochondrial DNA (mtDNA) in liver of rats and mice. DR is likely to decrease ROS production and has been shown to reduce the rate of DNA damage as evidenced by accumulation of oxo^{8}dG in various tissues (63-64). The efficacy of CR, particularly interventional clinical trials and the mode of such treatments for increasing health-span and life expectancy in humans, are still required before such strategies can be successfully implemented in humans.

2.2. NAM, NMN, NR, NAD$^+$ and metformin

The flow of carbon and energy occurs through glycolysis and mitochondrial oxidative phosphorylation (OXPHOS). These reactions require a tightly controlled balance between the synthesis and degradation of nicotinamide adenine dinucleotide (NAD) or NAD$^+$ in cells. NAD$^+$ is an important co-factor in all living cells and is essential to life in biological processes as diverse as production of ATP via anaerobic glycolysis, tricarboxylic acid cycle metabolism (Krebs cycle), OXPHOS, fatty acid β-oxidation, cell signaling, gene expression, and DNA damage repair by NAD$^+$-dependent sirtuins (65-71). In mammals, NAD$^+$ is synthesized from one or more of its major precursors including tryptophan (Trp), nicotinic acid (NA), nicotinamide (NAM), nicotinamide mononucleotide (NMN), and nicotinamide riboside (NR). In mammals, NMN is a natural compound and an efficient NAD$^+$ precursor and is synthesized from nicotinamide, by the rate-limiting enzyme, nicotinamide phosphoribosyl transferase (Nampt) from nicotinamide, and 5′-phosphoribosyl-1-pyrophosphate (PRPP), or from NR by NR kinases (NRKs) by phosphorylation reaction and then it is converted to NAD$^+$ by NMN adenylyl transferases (NMNATs) (68).

The deacetylase activity of the sirtuin proteins and metabolic homeostasis is dependent on NAD$^+$ (72-76). NAD$^+$ is also required for metabolism and the actions of poly(ADP-ribose) polymerase proteins (PARPs), namely PARP1 and PARP2 in mammals, and acts as a DNA damage sensor for these polymerases, in the processes of protein deacetylation and poly-ADP-ribosylation (PARylation) (77-80). PARP-1 is a NAD$^+$-dependent ADP-ribosyltransferase, that oscillates daily by feeding. It has been shown that PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation whereas PARP2 regulates SIRT1 expression and whole-body energy expenditure (81-82). Consistent with NAD$^+$ being required for PARP action, inactivation of PARP1 increases tissue NAD$^+$ levels and activates mitochondrial metabolism (81). Interestingly, there is some evidence that links the PARPs to increase in life-span (83-84).

It has been shown that the level of NAD$^+$ drops with age in *C. elegans* and aged mice and such a decrease reduces longevity in *C* and conversely genetic or restoration of NAD$^+$ levels prevents metabolic changes associated with aging and leads to increased life-span in *C. elegans* (85-86). In this nematode, increase in levels of NAD$^+$ by PARP inhibitors leads to the improvement of mitochondrial homeostasis through the activation of the sirtuin homolog, sir-2.1 and leads to the activation of the mitochondrial unfolded protein response (UPR^{mt}), which is a mitochondrial proteostasis pathway, known to promote longevity (87-89). This increase also leads to the activation of the FOXO transcription factor, *daf-16,* triggering an antioxidant protection program (85, 90).

In mammalian cells, the principal substrate for the synthesis of NAD$^+$ is the nicotinamide (NAM) salvage pathway which requires sequential actions of nicotinamide phosphoribosyltransferase also known as pre-B-cell colony-enhancing factor 1 or visfatin (Nampt) and NMN adenylyltransferases (NMNAT1-3) leading to the production of NAD$^+$ from NMN and ATP (91). Thus, NAM is a requisite precursor for the

synthesis of NAD^+, a key molecule that maintains SIRT1 activity, energy metabolism, and metabolic homeostasis (68-69, 92-95). Aging and age-related diseases, including metabolic disorders, cancer and neurodegenerative diseases all result in reduced intracellular NAD^+ levels due to reduced synthesis and increased in its consumption. It has been shown that administration of NMN to rodents enhances the biosynthesis of NAD^+ in many tissues. Also, the administration of NAD^+ precursors, such as NAM, or nicotinamide riboside (NR) is an efficient way to substitute the lowered levels of NAD^+ that occur with age. In a mouse model of obesity, NAM has been shown, when added to a standard diet, to restore glucagon storage and to ameliorate diet-induced hepatosteatosis, oxidative stress and inflammation that is seen in age-matched mice (96). NAM improves mitochondrial function, prevents age and high fat diet induced DNA damage and inhibits formation of glucoma (96-97). Loss of NAD^+ can also be effectively remedied by long-term oral administration of NMN (up to 300 mg/kg) that has been shown to increase NAD^+ in various peripheral tissues in mice without causing toxicity, an strategy that offers protection against age induced functional decline as evidenced by erasing age-related changes in gene expression and adipose tissue inflammation and for replenishing energy stores, re-establishing insulin sensitivity, restoring mitochondrial oxidative and lipid metabolism, and in maintaining the eye and immune functions and bone density (68, 93, 98-108).

Overexpression of the mitochondrial *Nmnat3* in mice, which is required for NAD^+ biosynthesis, improves age induced glucose tolerance and high-fat induced obesity (109). NMN has been shown to prevent age related metabolic dysfunction, to increase insulin secretion and sensitivity and to normalize glucose tolerance in a host of conditions. NAD^+ dependent improvements in health-span has been shown in normal aging mice, *Nampt*$^{+/-}$ mice, β cell-specific *Sirt1*-overexpressing (BESTO) mice, age or diet-induced diabetes, and hypomorphic BubR1 (a mitotic check-point kinase) mice (68, 93-98, 108). In the *C. elegans* model of xeroderma pigmentosum group A, ataxia telangiectasia, that is caused by mutation in *ATM*, a master regulator of DNA damage response and which leads to severe neurodegeneration, NMN, affords protection against premature aging and extends life-span and health-span (85, 104, 109-117).

Treatment of mice with NMN (up to 300 mg/kg) has revealed no toxicity and NMN has been shown to readily pass the blood brain barrier increasing the NAD^+ levels in the brain tissues (118-120). In animal models of aging, long-term administration of NMN maintains lipid and energy metabolism, increases insulin sensitivity, protects the eye and immune functions, bone density and affords protection in the animals against age-associated functional decline (108). Administration of NMN reduces inflammation, improves mitochondrial function in arterial and skeletal muscles, maintains neural stems and progenitor cell population, prevents synaptic loss and protects aged mice against neuronal cell death, pathological damage by Alzheimer's disease associated β-amyloid (Aβ), cognitive function, and neurodegeneration (121-126). NMN protects the heart and brain against ischemia-induced damage (127-128).

In the salvage pathway, NR, a natural precursor of NAD^+, is converted into NMN by NRKs. NR protects against aging and age-related diseases, decreases weight gain and obesity, and improves glucose tolerance. In models of diabetes and high-fat diet, NR improves metabolic function and reduces fat deposition and increases life-span and health-span in many model systems (85, 129-137). Replenishing NAD^+ stores, by administration of 400 mg per kg NR, improved muscle function and reduced heart damage in mdx and mdx/Utr$^{-/-}$ mice and reversed pathology in *C. elegans* models of Duchenne Muscular Dystrophy (DMD) (138). Nampt skeletal muscle knockout mice show 85% decline in intramuscular NAD content, muscle fiber degeneration and progressive loss of muscle strength and exhibit a reduced treadmill endurance. In this model, the supplementation of NR, despite having a modest effect on the intramuscular NAD levels, reversed these functional deficits and restored muscle mass (139). NR has been shown to improve the mitochondrial proteostasis and functions and to maintain motor functions. NR also delayed the decline in cognitive function, improved learning and memory, and reduced the neuronal cell death in

animal models of AD and Parkinson's disease (PD). In *C. elegans* and AD mice, NR prevented the development and progression of Aβ pathology (140-143). In triple transgenic model of AD that causes DNA repair deficiency, NR prevented neuronal damage by phosphorylated tau, neuroinflammation, synaptic dysfunction and cognitive decline (142). NR has been shown to prevent mitochondrial defects, age-related dopaminergic neuronal loss and motor decline in fly models of Parkinson's disease, providing an avenue for neuroprotection in PD and other neurodegenerative diseases (140). As compared to nicotinic acid and nicotinamide, oral administration of NR elevated mouse hepatic NAD^+ with superior pharmacokinetics and in a 52 year old man, a single oral dose of 1000 mg NR increased, by 45.5 fold, the blood levels of nicotinic acid adenine dinucleotide (NAAD) which acts as a NAD^+ biosynthesis intermediate and increased NAD^+ by 2.7-fold (144). Treatment of these cells with NR, induced the mitochondrial unfolded protein response and synthesis of prohibitin proteins, and this rejuvenated these cells in aged mice. NR also improved mitochondrial function and prevented MuSC senescence in the mdx (C57BL/10ScSn-Dmd^{mdx}/J) mouse model of muscular dystrophy and prevented the senescence of neural and melanocyte stem cells and increased the life-span in mice (132). Reductions in NAD^+ in natural aging, which results from mitochondrial dysfunction, has been shown to impair muscle fiber integrity whereas supplementation of the NR has been shown to reverse the progressive muscle dysfunction in mice (145).

In a first clinical trial of pharmacokinetics of NR in humans, single doses of 100, 300 and 1,000 mg of NR, in 12 healthy subjects (ages 30–55 years old) produced dose-dependent increases in the blood NAD^+ metabolome, NAD^+ and NAAD levels, without inducing any adverse effects (145). In a double-blind and placebo-controlled study in 120 healthy adults (60–80 years old), NR (250 mg and 500 mg), did not evoke any toxicity and induced dose-dependent increase of blood NAD^+ levels after 4-weeks and these levels were sustained for the entire eight week duration of the study (146). In a similar double-blind, placebo-controlled study in 55–79 year old healthy subjects, NR administered orally at 500 mg, twice a day was well tolerated and effectively elevated NAD^+ levels, and reduce systolic blood pressure and aortic stiffness (147). These data, therefore, show that age related decline of NAD^+ and the associated age related pathologies can effectively be reversed by the substitution of NAD^+ by administration of NAM, NMN or NR.

AMPK is activated by nutritional restriction and CR as well as by metformin that has long has been used for the treatment of prediabetes and type 2 diabetes, and is currently being considered for the treatment of obesity, for its cancer effects, as an approach for prevention of cognitive impairment, dementia, and Alzheimer's disease as well as an anti-aging medicine (148-153). The adult dose of metformin for the treatment of diabetes is 2 grams (12 mmol) per day from which 6 mmol is excreted daily by the kidneys and the other half is lost in feces (154). Metformin is the most potent member of biguanides and is more effective than buformin and phenformin that appear to act through the mitochondrial complex I (155). Proteomic analysis has revealed that metformin upregulates degradation of branched-chain amino acids, the citrate cycle, glycolysis, and pyruvate metabolism (156). The mode of action of metformin has provided conflicting interpretations. Originally, meformin was suggested to be a "caloric restriction mimetic", acting similar to DR through the AMPK and LKB1, a view that is no longer considered viable (157). Metformin is thought to act similar to a mild uncoupler for ETC, blocking retrograde electron transport and peroxide production. In isolated mitochondria, 25 mM metformin completely inhibited complex I-driven O_2 flux and led to an increased ROS production. Metformin apparently binds to a putative specific carrier in the inner mitochondrial membrane that allows its enrichment from micromolar levels in the cytosol to millimolar levels in the mitochondrial matrix leading to an increase in ADP to ATP ratio (158-159). The phase III multi-site TAME (Targeting Aging with Metformin) trial has proposed metformin as an antiaging drug in model organisms (160-161). In *C. elegans*, fed with live *E. coli* subjected to 25 or 50 mM metformin life-span was increased by 13 to 36% (85). The authors concluded that, the effects of metformin was indirect, due to inhibition of the folate metabolism in the bacteria leading to nutrient deficiency resulting in decreased

availability of methionine and suppressed levels of S-adenosyl methionine (SAM) and decreased SAM/S-adenosyl-L-homocysteine (162-163).

Deletion of *prdx-2* gene, that belongs to a family of peroxidases, the so-called peroxiredoxins (EC1.11.1.15) abolished the effect of metformin on life-extension, and resulted in the death of the treated worms (164). According to others, metformin acts through "lysosomal" pathway and LKB1-AMPK and mTORC1 metabolic signaling networks. Metformin extended health-span as evident by reduced pigmentation and prevented age-related decline in fitness (locomotion body bends) and promoted life extension by activation of the orthologue of AMPK (AAK-2) in *C. elegans*. It is proposed that, metformin actions are directed at lysosomes, since metformin failed to increase life-span in lysosomal mutants (156). It has been suggested that the life-span extension in *C. elegans* by metformin involves AAK-2-dependent translocation of SKN-1 into the nuclei and increased activity of AAK-2 which requires presence of an intact AAK-2/AMPKα subunit and the SKN-1 transcription factor (157). However, meformin failed to extend life-span in the mutants that lacked the orthologues of LKB1 (*par-4*) or axin (*axl-1*) (165). Despite the fact that metformin increased activation of AMPK at 10 mM in the tissues of *D. melanogaster*, it did not extend their life-span (166-167). Also, the life extension by use of 0.1% metformin in male C57BL76 mice has not been reproduced (168-169). However, there are other data that support the notion that metformin extends life in *C. elegans, Drosophila,* rodents and humans, and it can prevent the development of cancer and cardiovascular diseases (149-150, 153, 170-171). Some of the effects of metformin could be mediated through inhibition of mTOR complex-1 function in an AMPK-independent manner via RagGTPase (172).

2.3. Inhibition of mTOR

Rapamycin (Everolimus or Rapamune) is a compound with antifungal, immunosuppressive, and antitumor properties (172-175). Rapamycin acts, in part, by forming a gain of function complex with the peptidyl-prolyl-isomerase, FKBP12, and inhibits signal transduction pathways which are required for cell growth and proliferation (176). However, in 1994, it was realized that the rapamycin-FKBP12 complex directly targets the mTOR (177-179). Pharmacological inhibition of mTOR by rapamycin has confirmed that the role of mTOR is evolutionarily conserved and it acts as a strong regulator of longevity in species as diverse as *S. cerevisiae*, *C. elegans*, *D. melanogaster*, to *Mus musculus* (181-182, 185-294). Administration of rapamycin, starting at 270 days of age, extended the life-span in normal mice by retarding aging, postponing death from cancer, or both and in short-lived mutant strains of mice, rapamycin extended their maximum life-span, nearly, by three-fold (194). The activity of mTOR was increased in hematopoietic stem cells (HSC) in old mice. This included increased in the abundance of the mRNA encoding the CDK inhibitors, p16 (Ink4a), p19 (Arf), and p21(Cip1) as well as a relative decrease in lymphopoiesis; and impaired capacity to reconstitute the hematopoietic system. In old mice, rapamycin increased life-span, restored the self-renewal and hematopoiesis of HSCs, and allowed for an effective vaccination against a lethal challenge with influenza virus. When mTOR was activated in the HSCs in young mice, the phenotypes of HSCs in old mice could be replicated (195). Sesamin, a polyphenolic compound in sesame seeds, has recently been reported to extend the life-span in *C. elegans* (196). Since the effects of seasmin on longevity was abolished by daf-15, which encodes the target of rapamycin (TOR)-binding partner, Raptor, it seems that it does not act through sir-2.1 or AMPK, rather, it signals through the unfolded protein response and mTOR.

2.4. Antioxidants

The free radical theory of aging attributes aging to the oxidative damage, therefore, it follows that the relief from oxidative damage by anti-oxidants should extend life-span (197). There is ample evidence that oxidative damages endured by macromolecules are reversible and such reversal prolongs the life-span. For example, overexpression of the antioxidant enzyme, catalase, significantly increased the life-span of the transgenic mice (198). There is a large number of anti-oxidants such as vitamin C and E, lipoic acid, coenzyme Q, melatonin, resveratrol, curcumin, polyphenols, and synthetic antioxidants including antioxidant nanoparticles.

Among these, vitamin C (ascorbic acid) is a powerful hydrophilic inhibitor of lipid peroxidation and inhibits propagation of free radicals (197). Vitamin E is a hydrophobic anti-oxidant that resides in cell membranes and is present in circulating lipoproteins. Indolepropionamide, is endogenous antioxidant, which reduces ROS, by binding to the rate-limiting component of oxidative phosphorylation in complex I of the respiratory chain (199). The geroprotector, Epitalon a synthetic tetrapeptide (Ala-Glu-Asp-Gly) that is known to have antioxidant activity, showed to increase life-span by 11-16% in *Drosophila melanogaster* (200-203).

The di-peptide, carnosine (beta-alanyl-L-histidine) which is found, by and large, in muscle and brain has a large number of pro-longevity effects (204). Carnosine acts as anti-oxidant and radical scavenger, as a neuroprotector against free radicals, has lipid-peroxidase and anti-inflammatory effects, quenches reactive carbonyl species, inhibits glycation of low-density lipoproteins that promote foam cell formation, has membrane stabilizing action, protects against ischemic damage, prevents telomeric damage and attrition, and has been shown to prevent age related decline in mitochondrial functions, and senescence of fibroblasts (205-216). Carnosine also increased cellular longevity and Hayflick limit and showed rejuvenating effect in human fibroblasts and increased the life-span by 20% in male and not female *Drosophila melanogaster* (216-218). The Trolox- (water-soluble analog of α-tocopherol) acylated derivatives (S,S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carbonyl-β-alanyl-L-histidine (S,S-Trolox-carnosine, STC), increased the life-span by 16% in males and 36% in female fruit flies (219). Carnosine suppressed the adverse effects of age-related disorders that show protein glycoxidation such as Alzheimer's disease and type-2 diabetes (220-225).

The stilbenoid polyphenol, resveratrol (3,5,4′-trihydroxy-trans-stilbene,), was originally isolated from the roots of white hellebore (*Veratrum grandiflorum, O. Loes*) and of *Polygonum cuspidatum.* Resveratrol is present in peanuts, blueberries, pine-nuts, and skin and seeds of red grapes, (or *Fallopia japonica*) (226-228). Resveratrol has been shown to have free radical scavenging and anti-oxidant, anti-inflammatory, anti-microbial, anti-carcinogenic, cardioprotective, neuroprotective, vasorelaxant, and phytoestrogenic effects (228). Resveratrol appears to promote vascular health in aging, yet, when was provided with a high protein diet to old mice, it increased the risk for cardiovascular system (229). Resveratrol has shown neuro-protective effects including decreased cholinergic neurotransmission and by preventing neuronal apoptosis. Resveratrol increased the expression of brain-derived neurotrophic factor, clearance of β-amyloid peptides and led to anti-amyloidogenic cleavage of APP in Alzheimer's disease (230).

There are bioactive compounds that are found in a diverse array of foods including olive oil, fish oil, vegetables, beans, nuts, and fruits. The bioactive polyphenol, curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (diferuloylmethane, CUR), is the main component of the yellow extract from the plant *Curcuma longa* (turmeric), a popular Indian spice (231-232). Curcumin is metabolized into its active metabolite, tetrahydrocurcumin (THC), by a reductase found in the intestinal epithelium that, as compared to other curcuminoids, has a strong antioxidant activity (233). Curcumin has anti-inflammatory properties by virtue of inhibiting activation of the inflammation factor, NFκB, and of the IκB kinase complex (IKK)(234). Curcumin also delays aging by inhibiting mTOR kinase (235-236). Curcumin might also retard aging by its actions on AMPK/UCP2 pathway (237). Curcumin, modulated the expression of age-associated genes, improved health span, and extended life-span in *Drosophila Melanogaster* (238).

Tyrosol which is a main phenol present in extra virgin olive oil has been shown to increase stress resistance and significant extension of life-span in *C. elegans*, possibly by its action on heat shock response (HSF-1) and the insulin pathway (DAF-2 and DAF-16) (239). Fisetin is a caloric restriction mimetic that has been shown to protect rat brain against aging induced oxidative stress, senescence, apoptosis and neurodegeneration (240-243).

Quercetin, present in red kidney beans, caper, radish and onion leads to an increase in

nuclear Nrf2 translocation and reduces Nrf2 ubiquitination (244). Quercetin has been shown to have anti-aging effects, to enhance spatial learning and memory, to protect against cognitive dysfunction, and diabetes (245-248). Epicatechin, is a natural flavonol that exerts its neuroprotective effects via activation of Nrf2/ARE and decreases traumatic brain injury and neuronal degeneration in mice (249). A large array of natural phytochemicals, that are present in fruits and vegetables, have shown promising Nrf2-ARE activating effect. This includes sulforaphane, curcumin, epigallocatechin gallate, allyl sulfides which are organosulfur compounds including diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) present in garlic, resveratrol, lycopene, capsaicin, 3H-1,2-dithiole-3-thione (d3t), 3-O-caffeoyl-1-methylquinic acid, brazilin, cafestol, carnosol, chaocone, and chlorophyllin (250). Omega-3 fatty acids, which are present in fish oil and flaxseed, also increase the nuclear translocation of Nrf2 (251).

There are data that show the damaged molecules might respond to the anti-oxidant treatment. For example, short term administration of N-*tert*-butyl-*α*-phenylnitrone (PBN) to aged gerbils reduced the protein carbonyls in brain, augmented the activity of glutamine synthetase, and normalized, the number of errors in radial arm maze patrolling behavior, to the values that were observed in young animals. However, these changes did not persist when the treatment was stopped (252). Similarly, treatment of old mice (17.5 months) with high-CoQ diet (2.81 mg/g) for 15 weeks led to reduced oxidative damage in proteins and concomitantly improved special performance in Morris water maze test (253).

In Hutchinson-Gilford progeria syndrome (HGPS), Mesenchymal Stem Cells (MSCs) fail to respond or survive the oxidative stress as a result of being able to mount an appropriate NRF2 response (254-259). NRF2-activating compounds such as oltipraz, have been shown to rescue the accelerated attrition of iPSC-derived MSCs in this type of progeria, showing that anti-oxidants are among the arsenals that can effectively be used to defend against oxidative damage in aging (260).

2.5. Hydrogen sulfide

In flies, the longevity benefits of DR can be erased, by adding back the EAA to food (53). Other DR regimens that restrict specific nutrients, including protein or EAAs, without periods of food restriction, also extend life-span and health-span in *Drosophila* to mice (261-263). One of the best examples of such a diet is methionine restriction that shows that this approach can also extend life-span effectively in yeast, worms, flies, rodents, and human cells in culture (163, 264-270). Restriction of cysteine also results in stress resistance, metabolic fitness and it causes 42% increase in mean and 44% increase in maximum life-span (271-275). Thus, restricting diet in sulfur amino acids (SAA) are equally effective in rendering the same impact as DR on longevity and such a diet is easier to be implemented by humans. The beneficial effects of SAA deprivation can be provided by an increase in the supply of the gasotransmitter, H_2S, to the body by consumption of garlic (37). DAS, DADS, and DATS in garlic, effectively release hydrogen sulfide (H_2S) after consumption (276). The allyl iso-thiocyanate, derived from Wasabi, mustard, Arugla and horseradish, which are known to exert many health benefits, are also effective means for increasing the level of H_2S in the body (277). Members of the Brassicaceae or Cruciferae, which are better known as the mustards, the crucifers, or the cabbage family, including arugula (Eruca sativa Mill), produce the iso-thiocyanate, sulforaphane, which has been shown to increase the release of H_2S *in vitro* (278). The sulfide in these cultivars, which is released by cooking, ranges from 0.02 to 0.39 ppm (278-280).

The clear image as how dietary restriction (DR) without malnutrition improves the life-span has emerged recently, and some of the molecular mechanisms that underlie such life extension have come to focus in the past few years (281). There are several lines of evidence that the transsulfuration pathway (TSP) is evolutionary conserved and that the H_2S improves glucose tolerance, increases stress resistance, is cytoprotective and has life extension properties. Hine *et al*, reported in 2015 that in a mouse model of DR-mediated stress resistance,

the restriction of SAA, cysteine and methionine, increased expression of the enzyme cystathionine γ-lyase (CGL, CTH or CSE) of the transsulfuration pathway (TSP), which increased H_2S production and protection from hepatic ischemia reperfusion injury (282-284). The positive impact of DR on stress resistance and on H_2S production was shown to be extinguished by SAA supplementation, mTORC1 activation, and chemical or genetic CGL inhibition. It has been shown that the TSP-dependent H_2S production is conserved in yeast, worm, fruit fly, and rodent models of DR-mediated longevity. Together, such findings have shown that H_2S production is essential to the positive effects of dietary restriction and that the impact of such a diet, at least in part, is due to the restriction of consumption of cysteine and methionine which, in turn, increases the production of H_2S.

The production of H_2S diminishes with age and thus, the protective effect of this gas gradually declines as the organism grows older. For example, it has been shown that there is an age-related decline in CGL and CBS expression and H_2S production in various tissues in rats. It has been shown that such a reduction can be prevented, by a long-term 10–40% CR, when instituted from 8 to 38 months of age (285). Short-term SAA restriction even for 1 week, has shown to increase hepatic CGL expression while a 5 week restriction of SAA has resulted in the elevated expression of hepatic CGL and CBS (286). 20–40% CR has led to a dose-dependent increase in hepatic H_2S production in mice and such an increase has been associated with an improved health, yet, not always it has led to an extended longevity (287-288). The reversal of age related decline in CGL and CBS expression and H_2S production in kidney has been shown in rats to be achievable by 30% CR (289). There is also a strong evidence that H_2S is involved in aging and its normal function is necessary for inhibiting free-radical reactions, activation of SIRT1, and probably by interacting with the age-related gene Klotho (290). H_2S has been shown to maintain the Klotho expression following acute kidney injury. The actions of H_2S are similar to, Klotho, which induces expression of manganese superoxide dismutase (SOD) and resistance to oxidative stress, by activating the forkhead transcription factors (FOXO) (291-292).

2.6. Senotherapeutics, senolytics, senomorphics and anti-inflammaging strategies

One of the prominent hallmarks of aging is the development of cellular senescence which occurs in aging tissues and contributes to the tissue or organismal aging, and to the diverse Age-Related Diseases (ARDs). Genetic ablation of senescent cells increases health-span and reduces the risk of age-related pathologies in mice. Thus, senotherapeutics is a new strategy for the removal of these cells as a fight against aging. Senotherapeutics include senolytics which selectively kill senescent cells and senomorphics which delay the progression of young cells to senescent cells in tissues, restore the functions of these cells to the levels found in young cells, or clear the senescent cells from tissues by immune-system mediators. Among these, rapamycin, which acts as an mTOR inhibitor, increased the median and maximal life-span of both male and female mice when was administered beginning at 600 days of age (293). Administration of rapamycin to mice, beginning at 270 days of age, also increased survival in both males and females. The pattern of the development of the disease, however, did not differ in rapamycin-treated mice as compared to those of control mice. There is further evidence that rapamycin, along with increasing the life-span, also increases the function of various stem cells (294-298). Aging is associated with an increase in mTOR activation in stem cells and progenitors of the hematopoietic system (296). Administration of rapamycin to old mice protected against the age-dependent decrease in the function and of increase of biomarkers of aging in hematopoietic stem cells. The life extension property of rapamycin could be attributed to the postponement of death from cancer, by slowing aging, or both. The effect of the rapamycin also appears to involve epigenetic reprogramming by prevention of loss of several histone marks that decrease with age namely, H3R2me2, H3K27me3, H3K79me3, and H4K20me2 (299). These data show a distinct role for mTOR signaling in the regulation of mammalian life-span, and that pharmacological extension of life-span in both sexes is possible by targeting the mTOR pathway.

The senescent cells cause a host of age related complications, namely production of ROS, inducing by-stander senescence in other cells, causing senescence-associated mitochondrial dysfunction (SAMD), release of inflammatory cytokines, the so-called Senescence-Associated Secretory Phenotype (SASP), and impairing immune surveillance (303). Consistent with the by-stander effect, transplanting a relatively small number of senescent cells into young mice, led to the spread of cellular senescence in host tissues and persistent physical dysfunction (304). Transplantation of even fewer senescent cells to old mice shortened health-span and life-span and reduced their survival (304). Although, normally, the senescent cells are removed from tissues, aging leads to impaired clearance of these cells and their progressive accumulation in aged tissues, in different species including rodents, primates and humans (305-309). Consistent with adverse effects of such cells in tissues, the inducible clearance of p16INK4a-positive senescent cells has been shown to delay natural and premature aging in mice (310-315). Thus, a new therapeutic regimen for aging is to effectively remove senescent cells from tissues or to reduce the impact of their SASP (316-319).

The first intervention involving use of senolytics used dasatinib, a protein tyrosine kinase inhibitor, and the plant flavonoid, quercetin (320). The activity of these two drugs was different. Dasatinib removed senescent human preadipocytes whereas quercetin was more effective against senescent human endothelial cells and mouse bone marrow-derived mesenchymal stem cells (BM-MSCs). The combination of both drugs, reduced the senescent cells and age related pathologies and increased health-span in chronologically aged mice, in mice that were exposed to radiation, as well as Ercc1$^{-/\Delta}$-progeroid mice. The combined administration of dasatinib and quercetin reduced age related pathologies including Alzheimer's disease, atherosclerosis, hepatic steatosis, osteoporosis, pulmonary fibrosis and cardiac aging (321-324). Other classes of senolytics include inhibitors of kinase pathways such as P13L/AKT (Fisetin), those that bind p53, impact several pathways (Piperlongumine, Quercetin-3-D-galactos), inhibit Bcl-2 (ABT-263, ABT-737, A1331852, A1155463), heat shock protein 90 (17-AAG Geldanamycin), or histone deacetylase (HDAC) (Panobinostat) and UBX0101 which acts as histone deacetylase (HDAC) inhibitor and targets MDM2/p53 and a modified FOXO4-DRI interfering peptide that targets p53/p21 and serpine (316, 325-326). Senolytics have shown a great promise in restoring lost functions in aging tissues. Acute or intermittent treatment of old and progeroid mice with the senolytic agent, fisetin, also has reduced senescence markers in multiple tissues, reduced age-related pathologies, and extended median and maximum life-span (325). The use of dasatinib plus quercetin as a senolytic cocktail, has led to the increase and selective clearance of senescent cells, and reduced secretion of proinflammatory cytokines in explants of human adipose tissue (304). Moreover, intermittent oral administration of senolytics to naturally aged mice and young mice that received senescent cells prevented loss of physical functions and increased survival by 36% and reduced their mortality hazard by 65% (304). Removal of senescent cells has also been shown to reduce age-associated phenotypes and to rejuvenate HSCs (310-314).

Given that senescent cells participate in normal physiology such as wound healing, placental function and embryo development, these cells are normally cleared from tissues by the immune cells. However, immunoscenecence reduces the efficiency of the immune mediated clearance by NK cells, CD4^{+} T cells and macrophages that identify the senescent cells by different targets that appear on the cell surface of these cells. This includes MICA, and ULBP2 expressed by replicatively, oncogene and DNA damaged induced senescent fibroblasts, dipeptidyl peptidase 4 (DPP4), NKG2D ligands and CD9 that is expressed in replicatively and doxorubricin induced human umbilical cord endothelial cells (HUVEC) and human dermal fibroblasts (327-331). The DPP4, which appears on the cell membrane of senescent fibroblasts, is considered to be targetable by the antibody-mediated NK cell-mediated cytotoxicity (332). Another approach is the administration of T cells that, by the expression of the NKG2D chimeric antigen receptor (CAR), can recognize NKG2D ligands on the surface of senescent cells (327).

Senomorphics do not lead to the apoptosis of senescent cells, rather, they reverse the senescent phenotype and oppose the senoinflammation and inflammaging. This includes a wide range of approaches and drugs that include CR, CR mimetics (CRM), antioxidants, anti-inflammatory agents, as well as activators of telomerase, sirtuin, autophagy and proteasome (328-337). The target for the therapeutics varies and include IKK/NFκB pathway (NBD peptide), JAK (Janus kinase) pathway (ruxolitinib), PDGF/FGF pathway (ESC-CM), TGFBR2/p21 pathway (Mmu-miR-291a-3p), ATM kinase (KU-60019), Progerin/lamin A/C (JH4) as well as a number of other drugs with unknown targets (Juglanin, Quercetin-3-O-β-D-glucuronide, (−)-Loliolide, Quercetagetin 3,4′-dimethyl ether) (316). The best approach to the suppression of age related inflammation is to adopt preventive measures which include those that retard the aging process namely, CR, DR, restraining the consumption of protein, and sulfur containing amino acids, metformin, resveratrol, NAD^+, NMN, NR, epimedium total flavonoids, and icariin. It is recommended that the diet be supplemented with zinc (Zn) which often times is low in the elderly. Zn is thought to modulate the immune-inflammatory response and to interact with inflammatory cytokines including interluekin (IL)-6, tumor necrsis factor (TNF)- α as well as heat shock protein 70 (HSP70)(338-340). It has been shown that individuals that are over 60, if treated with TNF antibody, are less prone to infections (341).

The anti-inflammaging response that the aging organism mounts to counter the inflammaging leads to an increase in the circulating level of cortisol with un-avaoidable consequences including gluconeogenesis, global immunosuppression, frailty induced by catabolic effects, muscle protein catabolism and wasting and bone resorption and osteoporosis (342). Dehydroepiandrosterone (DHEA) and its sulphated precursor, DHEA sulphate (DHEAS), which are secreted by ACTH driven production from adrenal glands and to less extent by the ovary and testis, oppose the negative effect of cortisol induced by the anti-inflammaging response. These hormones antagonize the effect of cortisol at the glucocorticoid receptor level, directly by suppressing their production or by virtue of downstream metabolites and by opposing the cortisol induced immunosuppression (343-344). The ovarian and testicular DHEA are converted to the estrogen and testosterone and, for this reason, can not contribute significantly to this response (345). Unfortunately, the levels of these beneficial hormones reach a peak in early adulthood and then decline sharply with age so that by age 70 they reach to 10-20% of their values in youthful individuals (346). Whereas, high cortisol levels are associated with increased death in patients who suffer stroke, heart failure, sepsis, and sarcopenia, the low concentrations of DHEAS are associated with diverse age related pathologies including cardiovascular disease, sarcopenia, osteoporosis and mortality (347-353).

2.7. Reactivation of telomerase

There are findings that show that shortening of the telomeres has a significant adverse impact on the life-span of replicatively active cells and that reversal of telomere shortening can extend the life-span. Age dependent loss of the telomere function, leads to p53 activation resulting in loss of tissue stem cell and progenitor functions, apoptosis, impaired proliferation and senescence, marked tissue atrophy and physiological impairment in many organ systems (354). The production of transiently or reversibly immortalized engineered cells with active telomerase that do not harbor oncogenic mutations appears to be safe and offers the possibility of treating a variety of chronic diseases and age related pathologies that emerge from telomere based replicative senescence. The expression of the catalytic subunit of human telomerase (hTERT), which restores telomerase activity has been shown to reduce senescence and to extend the life-span of many human cell types (355-361). The hTERT immortalized cells have a normal karyotype and normal functions such as normal cell cycle controls and functional p53, p21Cip1, and p16Ink4a/pRB checkpoints, and like normal cells are contact inhibited, and require growth factors for proliferation (362).

Telomerase deficient mice have been used to show the relationship of the decline of telomeres, mitochondria and stem cells during aging (363). Loss of telomeres and their un-capping leads to impaired

responses to tissue injury, progressive tissue atrophy, stem cell depletion, and ultimately to multi-system organ failure (363). A knock-in allele that encodes a 4-hydroxytamoxifen (4-OHT)-inducible telomerase reverse transcriptase-Estrogen Receptor (TERT-ER) under transcriptional control of the endogenous TERT promoter was used to examine the effect of reactivation of telomerase activity on halting or reversing the impacts of deficiency in telomerase activity. Reactivation of telomerase, extended telomeres, reduced DNA damage signaling, led to the proliferation of quiescent cells, and erased degenerative phenotypes in testes, spleens and intestines (364). The reactivation of telomerase in adult tissue stem cells that suffered from shortened telomeres reversed degenerative pathologies that were reminiscent of age related pathologies in multiple organs (364). This rejuvenating intervention does not appear to be associated with the loss of differentiated phenotypes.

By overexpressing HRP-1, a telomere-binding protein, the telomeric length was extended in *C. elegans* and these animals were shown to live longer. Moreover, the extension of life-span in these animals was due to the increased telomere length, and not due to the overexpression of HRP-1 (365). Inhibition of proliferation in the virus-transformed human fibroblasts, could be overcome by the ectopic expression of the wild-type reverse transcriptase protein (hTERT) of human telomerase (366). It was shown that the activity of reverse transcriptase of telomerase synergized with calorie restriction and extended health-span and life-span in mice (367). Telomerase was also shown to prevent the accelerated cell aging that occurs in fibroblasts of patients with Werner syndrome (368). Ideally, stem cells can be transiently forced to express hTERT until such time that the telomeres are sufficiently elongated, and, then, the rejuvenated cells can be returned to the aged individual to restore functions that are lost due to aging in stem cells. Clearly, before such a practice can enter the clinical arena, the efficacy, long term safety and the assessment of its oncogenic potential are required (369).

2.8. Prevention of stem cell exhaustion

A predominant feature of aging is a progressive decline in stem cell function that results from cumulative epigenetic alterations that ultimately halt tissue repair (370). Like other cells, human adult stem cells, are subject to telomere shortening, and the diverse epigenetic modifications that are involved in aging including global loss of H3K9me3, and changes in the nucleolus organizer region related to ribosomal DNA (NOR-rDNA) (371-378). The multi-potent progenitor cells from adipose tissue show age-dependent loss of self-renewal capacity and exhibit an increased tendency to undergo adipogenesis (379). Bone-marrow-derived mesenchymal stem cells (MSCs) of patients with Hutchinson–Gilford progeria syndrome, are defective in their ability to differentiate (380). Similarly, the MSCs show loss of proliferation and differentiation potential, increase in senescence and loss of capacity to differentiated in aged animals (381-383). In many model organisms, the senescence and exhaustion of stem cells have been shown to be due to dysregulation of metabolic and nutrient-sensing pathways. Among these, decreased serum levels of insulin growth factor (IGF)-1 appears to promote stem cell quiescence, whereas, maintenance of these systems promotes proliferation of adult stem cells.. For example, repletion of NAD^+ in stem cells, improved mitochondrial and stem cell functions and enhanced life-span in mice (384). Moreover, introducing germ-line stem cells to *C. elegans* extended their life-span and implantation of neural stem cells extended life-span in Niemann-Pick C1 mice (385-386). Thus, it is clear that approaches that are designed to prevent age related decline in aging, such as prevention of exhaustion of stem cell pool, are one of the ways to extend human life-span.

Notably, overexpression of the enzymatic subunit of telomerase, TERT, in mice, on a cancer-resistant background or late in life, increased median life-span, suggesting that the length of telomeres and life-span are intimately linked (387-388). The self-renewal, and regenerative potential of HSCs are maintained by fasting and CR through modulation of the signaling through IGF1-PKA, mTORC1 and SIRT1 pathways and DR has been used to effectively rejuvenate the activity of muscle and intestinal stem cells (389-390). It has been shown that the life can be extended in progeroid mice and degenerative phenotypes can be prevented by the transfer of muscle-derived stem cells (MuSC) from young mice

(391). In a mouse model of progeria, muscle-derived stem/progenitor cells (MDSPCs) were defective in proliferation and multi-lineage differentiation. The intraperitoneal administration of MDSPCs from young wild-type mice, to progeroid mice restored proliferation and differentiation defects of aged MDSPCs and led to a significant rescue from degenerative changes and vascularization defects in tissues and increased in health-span and life-span. The rejuvenating effect of the stem cells from healthy young animals appears to be due to secretion of soluble factors. For example, systemic factors from young mice have been used to rescue the dysfunction of neural and muscle stem cells in old mice (392-393).

Three chemicals which are all known activators of the nuclear factor erythroid 2-related factor (NRF2) pathway, metformin, resveratrol and Oltipraz, stimulated the proliferation of pre-senescent hMSCs in the WS that induces progeria (394). By increasing the interaction between SIRT1 and Lamin A, resveratrol has shown promising effects by opposing the decline in the adult stems and to increase life-span in mice with premature aging (395). To create stem cells with better quality, a single-nucleotide variation (A245G) was introduced in the NRF2 locus. This change improved NRF2 stabilization and transcriptional activation of its target genes, conferred resistance to neoplastic transformation, delayed cellular senescence, and led to the self-renewal activity, and a better regenerative ability of stem cells *in vivo* (396). By induced expression of NRF2 target genes, the FDA approved, oltipraz, has shown to reduce the accelerated exhaustion of iPSC-derived MSCs in HGPS (260). Similarly, by activating sirtuins, the NR which was shown to delay the induction of senescence in MuSCs and aging in adult stem cells, also has shown to extend life-span in mice (132). The beneficial effects of metformin on aging, by activating AMPK which has been shown in worms and mice, is currently being carried out in humans (7, 157, 377, 397). Vitamin C, which acts both as a redox regulator and an epigenetic modulator, and reduces ROS levels and loss of function, has been shown to increase proliferation of MSCs in a stem cell model of Werner syndrome (398-400).

3. REJUVENATION STRATEGIES

There are several approaches that can restore lost functions in aged cells and lead to the rejuvenation of tissues without the need to repress differentiation and generation of a pluripotent state. Moreover, there are now new evidence that the aging clock can be reset to an earlier time point by several strategies such a partial reprogramming, or by use of a drug cocktail comprised of metformin, GH and DHEA. We will examine the available models that supports the notion that aging reversal is feasible.

3.1. Resetting of the aging clock and reversal of aging

Gene expression, which is requisite to life and all facets of cellular functions, is controlled by the structure of chromatin and by the state of the epigenome (401-402). The epigenetic landscape and retention of older “immortal” strands and segregation of the new strands to the daughter cells, is known to be important to the cell fate, and differentiation decisions of stem cells (403). This raises the possibility that the state of chromatin and epigenome might also underlie, some if not all, aspects of aging. One of the best characterized epigenetic means for regulation of gene expression occurs by the methylation of the DNA that remains stable or even can be passed on to the next generation until such time, that based on the cellular needs, this state is modified by the demethylation processes. Based on analysis of 8,000 samples from 82 Illumina DNA methylation array datasets, that included 51 healthy tissues and cell types, Horvath *et al* showed that the DNA methylation status of 353 genes can predictably and accurately estimate the age of any tissue within a narrow 2 year margin (404-406). The possibility that, these methylation sites are not merely markers of aging but also cause aging, is a possibility that has not yet been ruled out. This DNA methylation age or Horvath or epigenetic clock has some inherent properties including being zero in embryonic and induced pluripotent cells (iPs). The epigenetic clock shows sequential changes with the passage number of *in vitro* cultured cells. Interestingly, the clock was a great predictor of heritable acceleration of age and could even be applied to the determination of the biologic age of tissues from chimpanzees.

Thus, it follows that measures that can reset the aging or epigenetic clock and even to set it to zero now can be reliably tested. Among such measures, nature itself has provided us with many clues and circumstances that suggest that the aging clock can be reset to an earlier time-point. However, opportunities that reset the aging clock to zero must be approached with a great caution since they may unleash the possibility that pre-existing DNA mutations may lead to carcinogenesis. Among such conditions are parabiosis, genetic reprogramming, forced induction of near stemness by periodic introduction of pluripotency genes, fertilization, somatic cell nuclear transfer (SCNT), young extracellular matrix, and blood factors such as growth and differentiation factor (GDF)11.

Since aging results in progressive increase in the cortisol/DHEAS ratio, one approach is to provide DHEA or DHEAS as a supplement, and conclusive trial data that such an approach is beneficial is just emerging (343, 408-410). Recently, a trial was carried out and the participants, initially, received for a week, recombinant growth hormone (hGH alone) (0.015 mg/kg/day) and then 50 mg/day DHEA in the second week and finally, these were administered with 500 mg/day metformin in the third week. At the fourth week, all doses were individualized based on particular response of each participant (411). This treatment led to the improved immunological response and risk indices and reversed the aging clock. The rate of reversal of the epigenetic aging relative to the actual chronological age accelerated from −1.6 year/year from 0–9 months to −6.5 year/year from 9–12 months. The GrimAge predictor of human morbidity and mortality persisted six months after the treatment was discontinued. This is the first report that the epigenetic age estimator of life-span can be reversed by an anti-aging strategy.

This study clearly points to the fact that aging is not fixed and similar to differentiation can be reset and that strategies that successfully rewind the clock likely resume normal function of organs, tissues and cells, and bear the potential to allow the stem cells to regain their regenerative potential with the hope to reverse age related organ and tissue declines and pathologies. There are natural circumstances such as fertilization that are consistent with the idea that nature has found ways to reset the aging clock to zero or preferably just to an earlier time-point consistent with the youthful state of embryos to young adults. Moreover, the rejuvenation can be achieved by epigenetic reprogramming that involves somatic cell nuclear transfer (SCNT) or generation of induced pluripotent cells (iPs). Other approaches include partial or episodic reprogramming, heterochronic parabiosis, or exposure of aged cells to a youthfull extracellular matrix. The only caveat is that aging is associated with the accumulation of mutations in nDNA and mDNA that are not be remedied by rejuvenation strategies, requiring development of personalized medicine by sequential and partial rejuvenation of tissues in a step-wise fashion or by removing the unwanted mutations by clustered regularly interspaced short palindromic repeats (CRISPR). Also, we, so far, lack knowledge on sustainability and endurance of the available strategies, requiring the understanding that how often such rejuvenating regimens must be re-introduced.

3.2. Fertilization and somatic cell nuclear transfer (SCNT)

Epigenetic changes are indispensable to life and represent reversible processes by which response to environmental and developmental cues are received, leading to alterations of the DNA and histones by a host of enzymes such as methyltransferases, demethylases, acetyltrans-ferases, and deacetylases (412-414). Many enzymes, that modify chromatin, lack intrinsic DNA binding specificity and require special docking sites on chromatin, or are actively recruited by long and short noncoding RNAs or sequence-specific transcription factors (415-418). The so-called "*cis*-epigenetics" lead to transcription of genes that determine the cell fate and lock cells in a differentiated state (416). The gene expression is controlled by the extent of cytosine methylation of the regulatory regions of the genes, with heavy methylation, oftentimes, leading to repression of gene expression. These changes also include the modifications in chromatin state induced by methylation or acetylation of histones that can turn on (histone acetylation or histone 3 trimethylated at

lysine 4; H3K4me3) or turn off (histone 3 trimethylated at lysine 27;H3K27me3) the transcriptional activity of genes on demand (412, 419). The regulation of gene expression may also be achieved by a host of RNAs and proteins such as transcription factors, the so-called "*trans*-epigenetics" (416, 420). The epigenetic changes are normally stable and not prone to change by environmental cues, a process referred to as "canalization" (421). Despite being stable, the epigenetic modifications are not hard-wired and can be passively modified, for example, by sequential cell divisions that can be reinforced by specific enzymes that endow cells with a new epigenetic state (412, 422). DNA methylation changes occur and correlate well with the age of tissues. In fact, the DNA methylation status of some loci in any tissue including blood has been found to be sufficient to accurately assess the biologic age of the tissue and serve as a better predictor of the mortality than any other risk factor (404, 423-424).

The available data suggest that epigenetic changes that drive the aging processes can reliably be reset via extensive epigenetic remodeling that starts at fertilization and continues during germline specification and early development. Early development is associated with two major waves of epigenetic reprogramming, one that occurs at fertilization and, the other, later during germ cell development and imprinting (425). Fertilization acts as s potent mechanism for resetting of the aging clock by "reprogramming," of the zygotic nucleus by the factors that reside within the egg cytoplasm. In humans, this process is initiated immediately after fertilization and at the moment that the sperm head enters the ooplasm. After fertilization, the genome undergoes epigenetic reprogramming that entails genome wide modifications of 5-methylcytosine and DNA repair (425-426). The resetting of all age related changes in ovum is required to allow for resetting of the epigenetic landscape that gives rise to another organism with a normal life-span. The zygotic genomic reprogramming is unique since it entails the formation of so-called bivalent domains that include both H3K4me3 (active) and H3K27me3 (repressive) marks that remain on standby until activated (427). Chromatin marks are not spared from changes that typically occur in the enhancer elements marked by histone H3 monomethylated on lysine 4 (H3K4me1). This state correlates well with increased levels of chromatin interactions, whereas loss of this histone modification, leads to reduced levels of chromatin interactions (428). These enhancers get activated during differentiation of embryonic stem cells by virtue of modification of histone H3 lysine 27 from trimethylation (H3K27me3) state to an acetylated (H3K27ac) format (429-430). Although the rate of aging in germ cells and their biologic age might differ from the changes that occur in somatic cells, germ cells are not immune from cellular and molecular assaults of aging (431-432). Early during the development, with the notable exception of imprinted loci, primordial germ cells also reset the methylation marks of their genome, reaching a state of global hypomethylation that is stably retained. Methylation levels reach to their lowest levels in the developing embryo before gastrulation (433).

The notion that egg cytoplasm has rejuvenating effect, was a prelude to the concept to achieve cloning by somatic cell nuclear transfer (SCNT). This process involves removal of the nucleus of a differentiated somatic cell and its transfer to the cytoplasm of an enucleated oocyte (434-435). The first successful attempt was carried out by the introduction of nuclei from cells of blastula to the enucleated cells of a frog. The rationale for this choice was that it was known that all the nuclei of the blastula were equivalent. These early experiments clearly showed that nuclear transplants into eggs can give rise to normal embryos. Later, it was shown that egg transplantation of nuclei of endoderm cells of *Xenopus laevis* could give rise to swimming tadpoles that appeared to be entirely normal and at least 30% of nuclei of the blastula and at least 4% of gut-cell nuclei from hatched tadpoles contained all the required genetic information for the formation and functioning of a normal adult organisms (436-438). However, frogs which were derived from the nuclei of differentiating cells, exhibited more abnormality than those which were derived from embryonic cells. For example, 7 out of 27 frogs that were derived by the transfer of the nuclei of the gut cells of the hatched tadpoles were sterile. Although, initially, the offsprings were derived from SNCT of nuclei of early embryos, or embryo-derived cells during primary culture, ultimately, SCNT was successfully carried out by transplanting the nuclei from the mammary

glands of a sheep to an enucleated egg. These early attempts, ultimately, gave rise in 1996, to the birth of the first mammalian cloned animal, the Dolly (439). Dolly was fertile and gave rise to triplets, Lucy, Darcy and Cotton in the year 2000. At the age of 4, Dolly developed arthritis and was euthanized due to the development of disabling arthritis and lung carcinoma. However, this landmark achievement led to an entire field of cloning and provided the proof of hypothesis that the state of the DNA or epigenome of an adult cell is not a barrier to the generation of a normal adult and that nuclei of differentiated somatic cells can successfully revert to a totipotent state. Given that most cloned animals die, it is clear that the resetting of the aging clock and epigenetic reprogramming do not fully replicate the reprogramming that occurs in fertilized eggs (440).

These early studies clearly showed that the nuclei of aged differentiated cells can successfully give rise to embryos that become fertile adults and that the aging within such nuclei is not a hindrance to the reprogramming and resetting of the DNA, to a more youthful state, once placed within the rejuvenating environment of the ooplasm. Despite the fact that the age related changes and pathologies accumulate through a life-time, they are not passed to new generations. Each life begins with both the chronological and biological age being re-wound and set to zero and, moreover, there is evidence that longevity can be inherited and even be imprinted (441). Thus, reversal, or “resetting to zero,” of the aging clock appears to be deeply embedded in the nature of life.

3.3. iPSC and epigenetic reprogramming

As stated, the epigenetic marks, for example, the DNA methylations, are often very stable and not subject to change and reprogramming (442-443). Yet, the cell fate has been shown to be reversible through trans-differentiation or by SCNT. The epigenetic changes were also achieved, merely after 2 days, by the conversion of lymphocytes to muscle fibers by formation of heterokaryons of B lymphocytes and C2C12 myotubes (444-445). This conversion required the extinction of the lineage-specific lymphocyte associated gene repertoire by histone deacetylase (HDAC) activity and establishment of expression of muscle specific genes. Interestingly, the fusion of fibroblasts with human embryonic stem cells (hES) created tetraploid cells that exhibited the morphology, growth pattern and molecular signature of hES cells. Moreover, in ES cell hybrids, differentiation was extinguishedm, and, stemness rewired the cell fate, towards the stem cell programs and pluripotency (446-447). One possible explanation for this overriding effect of the somatic cell differentiation programs, lies in the *trans*-epigenetic enforcement that establishes a strong foothold on the maintenance of the ESC state by virtue of the fact that, the transcription factors that convey stemness, co-occupy not only their own enhancer elements but also the enhancers of other members. These pluripotency factors also bind and activate and suppress set of genes which are essential to the pluripotent state. For example, recent evidence has coupled the expression of Xist and the in-activation of X-chromosome to the expression of pluripotency. To achieve gene dosage parity between the sexes, the long non-coding expression of Xist mRNA is required for transcriptional silencing of one of the two X chromosomes in female cells. Oct4 (Pou5f1), Nanog and Sox2 are shown to lie at the top of the XCI hierarchy, and to regulate XCI by triggering X-chromosome pairing and counting. Thus, it becomes evident that that, genetic factors that underlie pluripotency, jointly repress Xist and couple X inactivation reprogramming to the control of pluripotency during embryogenesis (448-449).

The early work by forming heterokaryons, led to the landmark work of Shinya Yamanaka who demonstrated that differentiation is not fixed and can be reversed by generation of cells that are pluripotent (iPS) by introduction of merely four transcription factors, Oct4, Sox2, Klf4, and cMyc (OSKM), that reset the differentiation programs (450). Such dramatic reversal suggests that developmentally established epigenetic marks as well as epigenetic landscape of aging cells can all be erased and reversed. This is evident by rejuvenation of chromatin state of cyclin-dependent kinase inhibitor, p16 (*CDKN2A*) locus, which is progressively expressed with age, and causes the cell cycle arrest and senescence (426, 451). The idea that the aging clock is reset to zero in iPs cells became evident when it was shown that these cells can give rise to germline

cells as well as embryos (453). These studies showed that the global gene expression as well as chromatin states of iPs cells are remarkably similar to those in embryonic stem cells (ESC) and that indeed the resetting of the aging clock is feasible merely by introduction of Oct4, Sox2, cMyc and Klf4 transcription factors in the terminally differentiated cells (454). Many of these epigenetic changes that occur during the formation of iPs cells are remarkably similar to those which occur in the early zygote (455). Thus, it follows that transit of somatic cells to pluripotency, not only extinguishes the differentiated state and render these cells pluripotent, it allows these cells to be differentiated to other cells such as hematopoietic stem cells (HSCs) or neural stem cells (NSCs) that are rejuvenated (456). In contradistinction, direct conversion of fibroblasts to NSCs failed to reverse aging in the modified cells (457).

The un-winding of the aging clock, has provided the unique opportunity to consider that, by introduction of iPs, produced from any aging individual to the same person, tissues can be generated that are more youthful, and provide the unique opportunity to potentially extend their lives. However, such an initial enthusiasm was tempered by the fact that the iPs cells lead to the formation of teratomas, a side-effect that appears to be due to the tumorigenic effect of cMyc (458). This led to the consideration to eliminate cMyc from the reprogramming cocktail and to induce reprogramming with merely three transcription factors Oct4, Sox2, and Klf4 (459). Senescent cells from centenarians or cells derived from patients with HGPS have successfully been reprogrammed and the reprogramming has led to an increase in telomeric length, and a more youthful gene expression profile, and reduced oxidative stress (257, 259-260). Restoration of fibroblasts of patients with HGPS also lends further support that, reprogramming, dramatically improves cellular functions (261-265). However, there are considerations that appear to be obstacles to the clinical usefulness of this approach. This includes heterogeneity and in-efficiency (<1–2%) of this process, likely due to the potency of p16 and p53 that act as barriers to the formation of iPs. Moreover, the time consuming aspect of generation of iPs is a hindrance for introducing the idea as a clinical treatment for the reversal of aging (445, 452, 466). Moreover, the iPs generation may not restore the length of the telomeres nor full telomerase activity (467-468). Thus, before such technologies become therapeutically feasible, there is a need to fully understand how to improve the process, so that the reprogrammed cells become more equivalent to youthful cells and to insure that such cells are not the harbinger of tumorigenicity. The rejuvenation through iPs, perhaps can be substituted by other means that do not require the differentiated cells to fully relinquish their fate by forcing a mere partial or episodic reprogramming or through inhibition of the main culprits of aging programs such as by inhibiting the NFκB or mTOR, by inducing conditions similar to heterochronic parabiosis or by virtue of endowing youth through signaling from young extracellular matrices.

3.4. Partial reprogramming

To avoid the undesirable effects of full reprogramming, and more importantly, to avoid its tumorigenic potential, and yet to realize its beneficial impacts, an alternative approach for reversing age related pathologies has emerged. Given that reversal of age-associated cellular phenotypes has already been achieved *in vitro* by cellular reprogramming, some have resorted to the partial programming using the Yamanaka (OSKM) factors (460, 464-472). Ocampo *et al,* showed the effectiveness of partial reprogramming using a mouse model of premature aging (473-475). The premature aging (progeria), in this model, is due to a G609G mutation in the *Lmna* (LAKI) gene that leads to the accumulation of a faulty truncated form of lamin A (progerin) that disturbs the architecture of nuclear envelope and is also the cause of the human HGPS (476-477). These, so-called LAKI mice, show progeria along with weight loss and age associated damages in many organs. The partial reprogramming was achieved by the cyclic doxycycline responsive *in vivo* induction of OSKM factors and such induction led to the reversal of the aged cell phenotypes and alleviated pancreatic and muscle damages. The partial reprogramming failed to induce the pluripotency marker, Nanog, even after 12 days, suggesting that the reprogramming was not complete. Despite this, there was

remarkable reversal of age related damage including reduction of p53 binding protein 1 (53BP1), which participates in the DNA damage response as well as downregulation of the expression of p53 mediated age-related stress response genes, namely, p16INK4a, p21CIP1, Atf3, and Gadd45B, as well as the senescence-associated metalloprotease, MMP13 and interleukin-6. The partial reprogramming successfully restored the levels of H3K9me3 and H4K20me3 which drop with aging and significantly improved the architecture of nuclear envelope. Besides such changes at cellular and molecular levels, there were improvements in external appearance of these mice such as reduced spine curvature (kyphosis), and restoration of histologic appearance of tissues of major organs, thickening of skin, reduced involution of the white pulp within spleen and lymphoid tissues, decrease in tubular atrophy within kidneys and a significant increase in the median or maximal life-span. More importantly, these reversal of aging phenotypes were not associated with tumor formation nor were permanent, and, within 4-8 days, they were reversible as evidenced by the return of the H3K9me3 modification, and recurrence of nuclear envelope abnormalities. Together, such changes provided the proof of the hypothesis that short term induction of the reprogramming is sufficiently robust to reverse the age related damages that are evident at the tissue, cellular and molecular levels.

One drawback of this initial study was that premature aging model does not faithfully replicate natural aging. For this reason, a non-integrative reprogramming protocol was carried out on tissues from aged mice as well as aged human cells (478). The cocktail was comprised of mRNAs expressed from OCT4, SOX2, KLF4, c-MYC, LIN28, and NANOG (OSKMLN). Reprogramming factors were only transiently applied and then stopped (before the so-called Point of No Return, or PNR). Transcriptomic profiles, indeed, verified that the cell identities were retained after treatment. The epigenetic repressive mark H3K9me3, the heterochromatin-associated protein, HP1**γ**, and the nuclear lamina support protein, LAP2α, showed a decrease in the nuclei of aged fibroblasts and endothelial cells. The formation of autophagosomes, and chymotrypsin-like proteasomal activity, telomere's length, mitochondrial membrane potential and SIRT1 protein levels were increased while the ROS production, the senescence associated beta galactosidase and SASP phenotypes were decreased. Most notably, transient expression of OSKMLN led to the reversal of the epigenetic clock of human somatic cells, including endothelial cells and fibroblasts indicating that methylation age was reversed, respectively, by 1.62 years and 1.07 years. Chondrocytes derived from cartilage of six, 60–70-year-old patients, who suffered advanced stage of osteoarthritis as well as chondrocytes from young individuals were treated with the OSKMLN cocktail. This, treatment did not change the cellular identity of these cells as evidenced by expression level of SOX9, a transcription factor that defines the chondrocytic identity and function and significantly increased the expression of cartilage specific, COL2A1. Whereas, the RNA levels of antioxidant, SOD2, and ATP levels increased, this treatment led to a significant reduction of intracellular mRNA levels of RANKL and iNOS2, as well as in the levels of inflammatory factors secreted by these cells. Transient reprogramming of mouse-derived skeletal muscle stem cells (MuSCs), reduced the time of first division that became similar to the time required for the activation of quiescent young MuSCs and increased the ability of single MuSCs to form colonies and to differentiate into myotubes including their resumed regeneration potential *in vivo*. This treatment also led to the restoration of forced production by muscles that were transplanted with untreated aged MuSC. Similar results were obtained by using transplanted, transiently reprogrammed, aged human MuSCs that resulted in increased longitudinal bioluminescence imaging signals compared with untreated MuSCs from the same individual, and comparable with those observed using young MuSCs. There were not any evidence of neoplastic lesions or teratomas during the necropsy of the animals (478). These studies successfully showed that age related pathologies are reversible by partial reprogramming and that such a strategy leads to the reversal of aging clock. Given that the identities of the treated cells did not change with such treatments, it is evident that reprogramming can be distinctly uncoupled from the de-differentiation events and emergence of stem cell traits which have, thus far, been a major hurdle for

the use of reprogramming of cells and tissues in aging organisms.

4. CONCLUSIONS

Within the last two centuries, we have witnessed a great deal of progress in understanding the cell-centric causes of aging. Based on these diverse theories of aging, just in the past few decades, many therapeutic options have emerged that all have contributed to extend the health-span and life-span of model organisms to human beings. We have been able in regulating the aging process by manipulating the telomeres, and the signaling pathways, and have developed technologies to remove or restore the senescent cells within aging tissues. We have been able to force the differentiated cells to gain pluripotency and have used partial reprogramming in restoring the epigenome, to an earlier, more youthful state. Metformin and NAD^+ are at the forefront of aging therapeutics and the idea that a mixture of DHEA, GH and metformin can reset the aging clock, has opened new possibilities to even reverse the aging processes. We are certain that the trajectory of our understanding of aging will significantly increase in the next decade and new modes of treatment for aging, undoubtedly, will be unveiled.

5. REFERENCES

1. Kenyon CJ. The genetics of ageing. Nature. 464:504-512. (2010)
DOI: 10.1038/nature08980
PMid:20336132

2. Fontana L, Partridge L, Longo VD. Extending healthy life span-from yeast to humans. Science. 328:321-326. (2010)
DOI: 10.1126/science.1172539
PMid:20395504 PMCid:PMC3607354

3. Kimura KD, Tissenbaum HA, Liu Y, Ruvkun G. daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans. Science. 277:942-6. (1997)
DOI: 10.1126/science.277.5328.942
PMid:9252323

4. Apfeld J, O'Connor G, McDonagh T, DiStefano PS, Curtis R. The AMP-activated protein kinase AAK-2 links energy levels and insulin-like signals to lifespan in C. elegans. Genes & development. Dec 15 18. (24):3004-9. (2004)
DOI: 10.1101/gad.1255404
PMid:15574588 PMCid:PMC535911

5. Kenyon C. A conserved regulatory system for aging. Cell. Apr 20;105(2):165-8. (2001)
DOI: 10.1016/S0092-8674(01)00306-3

6. Tissenbaum HA, Guarente L. Increased dosage of a sir-2 gene extends lifespan in Caenorhabditis elegans. Nature. Mar;410(6825):227-30. (2001)
DOI: 10.1038/35065638
PMid:11242085

7. Mair W, Morantte I, Rodrigues AP, Manning G, Montminy M, Shaw RJ, Dillin A. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. Nature. Feb;470(7334):404-8. (2011)
DOI: 10.1038/nature09706
PMid:21331044 PMCid:PMC3098900

8. Kaeberlein TL, Smith ED, Tsuchiya M, Welton KL, Thomas JH, Fields S, Kennedy BK, Kaeberlein M. Lifespan extension in Caenorhabditis elegans by complete removal of food. Aging cell. Dec;5(6):487-94. (2006)
DOI: 10.1111/j.1474-9726.2006.00238.x
PMid:17081160

9. Lee GD, Wilson MA, Zhu M, Wolkow CA, De Cabo R, Ingram DK, Zou S. Dietary

deprivation extends lifespan in Caenorhabditis elegans. Aging cell. Dec;5(6):515-24. (2006)
DOI: 10.1111/j.1474-9726.2006.00241.x
PMid:17096674 PMCid:PMC2546582

10. Gallinetti J, Harputlugil E, Mitchell JR. Amino acid sensing in dietary-restriction-mediated longevity: roles of signal-transducing kinases GCN2 and TOR. Biochemical Journal. Jan 1;449(1):1-0. (2013)
DOI: 10.1042/BJ20121098
PMid:23216249 PMCid:PMC3695616

11. Longo VD, Antebi A, Bartke A, Barzilai N, Brown-Borg HM, Caruso C, Curiel TJ, De Cabo R, Franceschi C, Gems D, Ingram DK. Interventions to slow aging in humans: are we ready? Aging cell. Aug;14(4):497-510. (2015)
DOI: 10.1111/acel.12338
PMid:25902704 PMCid:PMC4531065

12. Mirisola MG, Taormina G, Fabrizio P, Wei M, Hu J, Longo VD. Serine-and threonine/valine-dependent activation of PDK and Tor orthologs converge on Sch9 to promote aging. PLoS Genet. Feb 6;10(2):e1004113. (2014)
DOI: 10.1371/journal.pgen.1004113
PMid:24516402 PMCid:PMC3916422

13. Mair W, Piper MD, Partridge L. Calories do not explain extension of life span by dietary restriction in Drosophila. PLoS Biol. May 31;3(7):e223. (2005)
DOI: 10.1371/journal.pbio.0030223
PMid:16000018 PMCid:PMC1140680

14. Segall PE, Timiras PS. Patho-physiologic findings after chronic tryptophan deficiency in rats: a model for delayed growth and aging. Mechanisms of ageing and development. Jan 1;5:109-24. (1976)
DOI: 10.1016/0047-6374(76)90012-9

15. Ooka H, Segall PE, Timiras PS. Histology and survival in age-delayed low-tryptophan-fed rats. Mechanisms of ageing and development. Apr 1;43(1):79-98. (1988)
DOI: 10.1016/0047-6374(88)90099-1

16. Orentreich N, Matias JR, DeFelice A, Zimmerman JA. Low methionine ingestion by rats extends life span. The Journal of nutrition. Feb 1;123(2):269-74. (1993)

17. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. Aging cell. Jun;4(3):119-25. (2005)
DOI: 10.1111/j.1474-9726.2005.00152.x
PMid:15924568 PMCid:PMC7159399

18. Suzuki M, Wilcox BJ, Wilcox CD. Implications from and for food cultures for cardiovascular disease: longevity. Asia Pacific Journal of Clinical Nutrition. Jun 15;10(2):165-71. (2001)
DOI: 10.1111/j.1440-6047.2001.00219.x
PMid:11710359

19. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. Jun 6;153(6):1194-217. (2013)
DOI: 10.1016/j.cell.2013.05.039
PMid:23746838 PMCid:PMC3836174

20. Chatzianagnostou K, Del Turco S, Pingitore A, Sabatino L, Vassalle C. The

Mediterranean lifestyle as a non-pharmacological and natural antioxidant for healthy aging. Antioxidants. Dec;4(4):719-36. (2015)
DOI: 10.3390/antiox4040719
PMid:26783955 PMCid:PMC4712942

21. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM. Primary prevention of cardiovascular disease with a Mediterranean diet. New England Journal of Medicine. Apr 4;368(14):1279-90. (2013)
DOI: 10.1056/NEJMoa1200303
PMid:23432189

22. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. New England journal of medicine. Jun 21;378(25):e34. (2018)
DOI: 10.1056/NEJMoa1800389
PMid:29897866

23. García-Calzón S, Martínez-González MA, Razquin C, Arós F, Lapetra J, Martínez JA, Zalba G, Marti A. Mediterranean diet and telomere length in high cardiovascular risk subjects from the PREDIMED-NAVARRA study. Clinical Nutrition. Dec 1;35(6):1399-405. (2016)
DOI: 10.1016/j.clnu.2016.03.013
PMid:27083496

24. Masana MF, Koyanagi A, Haro JM, Tyrovolas S. n-3 Fatty acids, Mediterranean diet and cognitive function in normal aging: A systematic review. Experimental Gerontology. May 1;91:39-50. (2017)
DOI: 10.1016/j.exger.2017.02.008
PMid:28213052

25. Nishihira J, Tokashiki T, Higashiuesato Y, Willcox DC, Mattek N, Shinto L, Ohya Y, Dodge HH. Associations between serum omega-3 fatty acid levels and cognitive functions among community-dwelling octogenarians in Okinawa, Japan: the KOCOA study. Journal of Alzheimer's Disease. Jan 1;51(3):857-66. (2016)
DOI: 10.3233/JAD-150910
PMid:26890763 PMCid:PMC4816662

26. Lettieri-Barbato D, Giovannetti E, Aquilano K. Effects of dietary restriction on adipose mass and biomarkers of healthy aging in human. Aging (Albany NY). Dec;8(12):3341. (2016)
DOI: 10.18632/aging.101122
PMid:27899768 PMCid:PMC5270672

27. Soare A, Cangemi R, Omodei D, Holloszy JO, Fontana L. Long-term calorie restriction, but not endurance exercise, lowers core body temperature in humans. Aging (Albany NY). Apr;3(4):374. (2011)
DOI: 10.18632/aging.100280
PMid:21483032 PMCid:PMC3117452

28. Fontana L, Klein S, Holloszy JO. Effects of long-term calorie restriction and endurance exercise on glucose tolerance, insulin action, and adipokine production. Age. Mar 1;32(1):97-108. (2010)
DOI: 10.1007/s11357-009-9118-z
PMid:19904628 PMCid:PMC2829643

29. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, Klein S, Ehsani AA, Holloszy JO, Washington University School of

Medicine CALERIE Group. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exercise-induced weight loss. Journal of Applied Physiology. Feb;102(2):634-40. (2007)
DOI: 10.1152/japplphysiol.00853.2006
PMid:17095635 PMCid:PMC4376253

30. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. Ageing research reviews. Oct 1;39:36-45. (2017)
DOI: 10.1016/j.arr.2016.08.005
PMid:27544442 PMCid:PMC5315691

31. Donati A, Recchia G, Cavallini G, Bergamini E. Effect of aging and anti-aging caloric restriction on the endocrine regulation of rat liver autophagy. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. Jun 1;63(6):550-5. (2008)
DOI: 10.1093/gerona/63.6.550
PMid:18559627

32. Wohlgemuth SE, Seo AY, Marzetti E, Lees HA, Leeuwenburgh C. Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and life-long exercise. Experimental gerontology. Feb 1;45(2):138-48. (2010)
DOI: 10.1016/j.exger.2009.11.002
PMid:19903516 PMCid:PMC2829942

33. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, Ingram DK, Lane MA, Mattson MP. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proceedings of the National Academy of Sciences. May 13;100(10):6216-20. (2003)
DOI: 10.1073/pnas.1035720100
PMid:12724520 PMCid:PMC156352

34. Varady KA, Roohk DJ, Hellerstein MK. Dose effects of modified alternate-day fasting regimens on *in vivo* cell proliferation and plasma insulin-like growth factor-1 in mice. Journal of Applied Physiology. Aug;103(2):547-51. (2007)
DOI: 10.1152/japplphysiol.00209.2007
PMid:17495119

35. Varady KA, Roohk DJ, Loe YC, McEvoy-Hein BK, Hellerstein MK. Effects of modified alternate-day fasting regimens on adipocyte size, triglyceride metabolism, and plasma adiponectin levels in mice. Journal of lipid research. Oct 1;48(10):2212-9. (2007)
DOI: 10.1194/jlr.M700223-JLR200
PMid:17607017

36. Yu BP, Masoro EJ, Murata I, Bertrand HA, Lynd FT. Life span study of SPF Fischer 344 male rats fed ad libitum or restricted diets: longevity, growth, lean body mass and disease. Journal of gerontology. Mar 1;37(2):130-41. (1982)
DOI: 10.1093/geronj/37.2.130
PMid:7056998

37. Hine C, Mitchell JR. Calorie restriction and methionine restriction in control of endogenous hydrogen sulfide production by the transsulfuration pathway. Experimental gerontology. Aug 1;68:26-32. (2015)
DOI: 10.1016/j.exger.2014.12.010
PMid:25523462 PMCid:PMC4464900

38. Lee BC, Kaya A, Gladyshev VN. Methionine restriction and lifespan control. Annals of the New York Academy of Sciences. Jan;1363:116. (2016)
DOI: 10.1111/nyas.12973
PMid:26663138 PMCid:PMC5008916

39. Hine C, Zhu Y, Hollenberg AN, Mitchell JR. Dietary and endocrine regulation of endogenous hydrogen sulfide production: implications for longevity. Antioxidants & redox signaling. Jun 1;28(16):1483-502. (2018)
DOI: 10.1089/ars.2017.7434
PMid:29634343 PMCid:PMC5930795

40. McCay CM, Maynard LA, Sperling G, Barnes LL. Retarded growth, life span, ultimate body size and age changes in the albino rat after feeding diets restricted in calories: four figures. The Journal of Nutrition. Jul 1;18(1):1-3. (1939)
DOI: 10.1093/jn/18.1.1

41. Ross MH. Length of life and nutrition in the rat. The Journal of nutrition. Oct 1;75(2):197-210. (1961)
DOI: 10.1093/jn/75.2.197
PMid:14494200

42. Ross MH. Length of life and caloric intake. The American journal of clinical nutrition. Aug 1;25(8):834-8. (1972)
DOI: 10.1093/ajcn/25.8.834
PMid:5046728

43. Ross MH, Bras G. Food preference and length of life. Science. Oct 10:165-7. (1975)
DOI: 10.1126/science.1166309
PMid:1166309

44. Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA, Bloom SR. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. American Journal of Physiology-Endocrinology And Metabolism. Jul 1;281(1):E155-61. (2001)
DOI: 10.1152/ajpendo.2001.281.1.E155
PMid:11404233

45. Fontana L, Partridge L. Promoting health and longevity through diet: from model organisms to humans. Cell. Mar 26;161(1):106-18. (2015)
DOI: 10.1016/j.cell.2015.02.020
PMid:25815989 PMCid:PMC4547605

46. Mattison JA, Roth GS, Beasley TM, Tilmont EM, Handy AM, Herbert RL, Longo DL, Allison DB, Young JE, Bryant M, Barnard D. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature. Sep;489(7415):318-21. (2012)
DOI: 10.1038/nature11432
PMid:22932268 PMCid:PMC3832985

47. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nature communications. Apr 1;5(1):1-5. (2014)
DOI: 10.1038/ncomms4557
PMid:24691430 PMCid:PMC3988801

48. Masoro EJ. Caloric restriction and aging: an update. Experimental gerontology. May 1;35(3):299-305. (2000)
DOI: 10.1016/S0531-5565(00)00084-X

49. Anderson RM, Bitterman KJ, Wood JG, Medvedik O, Cohen H, Lin SS, Manchester JK, Gordon JI, Sinclair DA. Manipulation of a nuclear NAD+ salvage pathway delays aging without altering steady-state NAD+ levels. Journal of Biological Chemistry. May 24;277-(21):18881-90. (2002)
DOI: 10.1074/jbc.M111773200
PMid:11884393

50. Bitterman KJ, Anderson RM, Cohen HY, Latorre-Esteves M, Sinclair DA. Inhibition of silencing and accelerated aging by nicotinamide, a putative

negative regulator of yeast sir2 and human SIRT1. Journal of Biological Chemistry. Nov 22;277(47):45099-107. (2002)
DOI: 10.1074/jbc.M205670200
PMid:12297502

51. Anderson RM, Bitterman KJ, Wood JG, Medvedik O, Cohen H, Lin SS, Manchester JK, Gordon JI, Sinclair DA. Manipulation of a nuclear NAD+ salvage pathway delays aging without altering steady-state NAD+ levels. The Journal of biological chemistry. Aug 16;288(33):24160. (2013)
DOI: 10.1074/jbc.A113.111773
PMCid:PMC3745358

52. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science. Jul 5;273(5271):59-63. (1996)
DOI: 10.1126/science.273.5271.59
PMid:8658196 PMCid:PMC2987625

53. Heilbronn LK, De Jonge L, Frisard MI, DeLany JP, Larson-Meyer DE, Rood J, Nguyen T, Martin CK, Volaufova J, Most MM, Greenway FL. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. Jama. Apr 5;295(13):1539-48. (2006)
DOI: 10.1001/jama.295.13.1539
PMid:16595757 PMCid:PMC2692623

54. Anderson RM, Shanmuganayagam D, Weindruch R. Caloric restriction and aging: studies in mice and monkeys. Toxicologic pathology. Jan;37(1):47-51. (2009)
DOI: 10.1177/0192623308329476
PMid:19075044 PMCid:PMC3734859

55. Veech RL, Bradshaw PC, Clarke K, Curtis W, Pawlosky R, King MT. Ketone bodies mimic the life span extending properties of caloric restriction. IUBMB life. May;69(5):305-14. (2017)
DOI: 10.1002/iub.1627
PMid:28371201

56. Masoro EJ. Overview of caloric restriction and ageing. Mechanisms of ageing and development. Sep 1;126(9):913-22. (2005)
DOI: 10.1016/j.mad.2005.03.012
PMid:15885745

57. Helfand SL, Rogina B. Genetics of aging in the fruit fly, Drosophila melanogaster. Annual review of genetics. Dec;37(1):329-48. (2003)
DOI: 10.1146/annurev.genet.-37.040103.095211
PMid:14616064

58. Rising R, Lifshitz F. Energy expenditures & physical activity in rats with chronic suboptimal nutrition. Nutrition & Metabolism. Dec 1;3(1):11. (2006)
DOI: 10.1186/1743-7075-3-11
PMid:16448560 PMCid:PMC1403780

59. Chacon F, Esquifino AI, Perello M, Cardinali DP, Spinedi E, Alvarez MP. 24-hour changes in ACTH, corticosterone, growth hormone, and leptin levels in young male rats subjected to calorie restriction. Chronobiology international. Jan 1;22(2):253-65. (2005)
DOI: 10.1081/CBI-200053522
PMid:16021842

60. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. Science. Sep 22;289(5487):2126-8. (2000)
DOI: 10.1126/science.289.5487.2126
PMid:11000115

61. Ramsey JJ, Colman RJ, Binkley NC, Christensen JD, Gresl TA, Kemnitz JW, Weindruch R. Dietary restriction and aging in rhesus monkeys: the University of Wisconsin study. Experimental gerontology. Dec 1;35(9-10):1131-49. (2000)
DOI: 10.1016/S0531-5565(00)00166-2

62. Weindruch R, Sohal RS. Caloric intake and aging. New England Journal of Medicine. Oct 2;337(14):986-94. (1997)
DOI: 10.1056/NEJM199710023371407
PMid:9309105 PMCid:PMC2851235

63. Barja G. Free radicals and aging. TRENDS in Neurosciences. Oct 1;27(10):595-600. (2004)
DOI: 10.1016/j.tins.2004.07.005
PMid:15374670

64. Hamilton ML, Van Remmen H, Drake JA, Yang H, Guo ZM, Kewitt K, Walter CA, Richardson A. Does oxidative damage to DNA increase with age? Proceedings of the National Academy of Sciences. Aug 28;98(18):10469-74. (2001)
DOI: 10.1073/pnas.171202698
PMid:11517304 PMCid:PMC56984

65. Magni G, Amici A, Emanuelli M, Orsomando G, Raffaelli N, Ruggieri S. Enzymology of NAD+ homeostasis in man. Cellular and Molecular Life Sciences CMLS. Jan 1;61(1):19-34. (2004)
DOI: 10.1007/s00018-003-3161-1
PMid:14704851

66. Verdin E. NAD+ in aging, metabolism, and neurodegeneration. Science. Dec 4;350(6265):1208-13. (2015)
DOI: 10.1126/science.aac4854
PMid:26785480

67. Katsyuba E, Auwerx J. Modulating NAD+ metabolism, from bench to bedside. The EMBO journal. Sep 15;36(18):2670-83. (2017)
DOI: 10.15252/embj.201797135
PMid:28784597 PMCid:PMC5599801

68. Yoshino J, Baur JA, Imai SI. NAD+ intermediates: the biology and therapeutic potential of NMN and NR. Cell metabolism. Mar 6;27(3):513-28. (2018)
DOI: 10.1016/j.cmet.2017.11.002
PMid:29249689 PMCid:PMC5842119

69. Canto C, Menzies KJ, Auwerx J. NAD+ metabolism and the control of energy homeostasis: a balancing act between mitochondria and the nucleus. Cell metabolism. Jul 7;22(1):31-53. (2015)
DOI: 10.1016/j.cmet.2015.05.023
PMid:26118927 PMCid:PMC4487780

70. Yaku K, Okabe K, Nakagawa T. NAD metabolism: Implications in aging and longevity. Ageing research reviews. Nov 1;47:1-7. (2018)
DOI: 10.1016/j.arr.2018.05.006
PMid:29883761

71. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. Cell metabolism. Mar 6;27(3):529-47. (2018)
DOI: 10.1016/j.cmet.2018.02.011
PMid:29514064 PMCid:PMC6342515

72. Imai SI, Guarente L. Ten years of NAD-dependent SIR2 family deacetylases: implications for metabolic diseases. Trends in pharmacological sciences. May 1;31(5):212-20. (2010)
DOI: 10.1016/j.tips.2010.02.003
PMid:20226541 PMCid:PMC3526941

73. Guarente L. Sir2 links chromatin silencing, metabolism, and aging. Genes

& development. May 1;14(9):1021-6. (2000)

74. Guarente L. Sir2 links chromatin silencing, metabolism, and aging. Genes & development. May 1;14(9):1021-6. (2000)

75. Haigis MC, Sinclair DA. Mammalian sirtuins: biological insights and disease relevance. Annual Review of Pathology: Mechanisms of Disease. Feb 28;5:253-95. (2010)
DOI: 10.1146/annurev.pathol.-4.110807.092250
PMid:20078221 PMCid:PMC2866163

76. Houtkooper RH, Cantó C, Wanders RJ, Auwerx J. The secret life of NAD+: an old metabolite controlling new metabolic signaling pathways. Endocrine reviews. Apr 1;31(2):194-223. (2010)
DOI: 10.1210/er.2009-0026
PMid:20007326 PMCid:PMC2852209

77. Schreiber V, Dantzer F, Ame JC, De Murcia G. Poly (ADP-ribose): novel functions for an old molecule. Nature reviews Molecular cell biology. Jul;7(7):517-28. (2006)
DOI: 10.1038/nrm1963
PMid:16829982

78. Asher G, Reinke H, Altmeyer M, Gutierrez-Arcelus M, Hottiger MO, Schibler U. Poly (ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding. Cell. Sep 17;142(6):943-53. (2010)
DOI: 10.1016/j.cell.2010.08.016
PMid:20832105

79. Gibson BA, Kraus WL. New insights into the molecular and cellular functions of poly (ADP-ribose) and PARPs. Nature reviews Molecular cell biology. Jul;13(7):411-24. (2012)
DOI: 10.1038/nrm3376
PMid:22713970

80. Amé JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, Muller S, Höger T, Ménissier-de Murcia J, de Murcia G. PARP-2, A novel mammalian DNA damage-dependent poly (ADP-ribose) polymerase. Journal of Biological Chemistry. Jun 18;274(25):17860-8. (1999)
DOI: 10.1074/jbc.274.25.17860
PMid:10364231

81. Bai P, Cantó C, Oudart H, Brunyánszki A, Cen Y, Thomas C, Yamamoto H, Huber A, Kiss B, Houtkooper RH, Schoonjans K. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell metabolism. Apr 6;13(4):461-8. (2011)
DOI: 10.1016/j.cmet.2011.03.004
PMid:21459330 PMCid:PMC3086520

82. Bai P, Canto C, Brunyánszki A, Huber A, Szántó M, Cen Y, Yamamoto H, Houten SM, Kiss B, Oudart H, Gergely P. PARP-2 regulates SIRT1 expression and whole-body energy expenditure. Cell metabolism. Apr 6;13(4):450-60. (2011)
DOI: 10.1016/j.cmet.2011.03.013
PMid:21459329 PMCid:PMC3108571

83. Grube K, Bürkle A. Poly (ADP-ribose) polymerase activity in mononuclear leukocytes of 13 mammalian species correlates with species-specific life span. Proceedings of the National Academy of Sciences. Dec 15;89(24):11759-63. (1992)
DOI: 10.1073/pnas.89.24.11759
PMid:1465394 PMCid:PMC50636

84. Mangerich A, Herbach N, Hanf B,

Fischbach A, Popp O, Moreno-Villanueva M, Bruns OT, Bürkle A. Inflammatory and age-related pathologies in mice with ectopic expression of human PARP-1. Mechanisms of ageing and development. Jun 1;131(6):389-404. (2010)
DOI: 10.1016/j.mad.2010.05.005
PMid:20561897

85. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cantó C, Mottis A, Jo YS, Viswanathan M, Schoonjans K, Guarente L. The NAD+/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell. Jul 18;154(2):430-41. (2013)
DOI: 10.1016/j.cell.2013.06.016
PMid:23870130 PMCid:PMC3753670

86. Gaur U, Tu J, Li D, Gao Y, Lian T, Sun B, Yang D, Fan X, Yang M. Molecular evolutionary patterns of NAD+/Sirtuin aging signaling pathway across taxa. PloS one. Aug 2;12(8):e0182306. (2017)
DOI: 10.1371/journal.pone.0182306
PMid:28767699 PMCid:PMC5540417

87. Yoneda T, Benedetti C, Urano F, Clark SG, Harding HP, Ron D. Compartment-specific perturbation of protein handling activates genes encoding mitochondrial chaperones. Journal of cell science. Aug 15;117(18):4055-66. (2004)
DOI: 10.1242/jcs.01275
PMid:15280428

88. Zhao Q, Wang J, Levichkin IV, Stasinopoulos S, Ryan MT, Hoogenraad NJ. A mitochondrial specific stress response in mammalian cells. The EMBO journal. Sep 2;21(17):4411-9. (2002)
DOI: 10.1093/emboj/cdf445
PMid:12198143 PMCid:PMC126185

89. Durieux J, Wolff S, Dillin A. The cell-non-autonomous nature of electron transport chain-mediated longevity. Cell. Jan 7;144(1):79-91. (2011)
DOI: 10.1016/j.cell.2010.12.016
PMid:21215371 PMCid:PMC3062502

90. Honda Y, Honda S. The daf-2 gene network for longevity regulates oxidative stress resistance and Mn-superoxide dismutase gene expression in Caenorhabditis elegans. The FASEB journal. Aug;13(11):1385-93. (1999)
DOI: 10.1096/fasebj.13.11.1385
PMid:10428762

91. Magni G, Amici A, Emanuelli M, Orsomando G, Raffaelli N, Ruggieri S. Enzymology of NAD+ homeostasis in man. Cellular and Molecular Life Sciences CMLS. Jan 1;61(1):19-34. (2004)
DOI: 10.1007/s00018-003-3161-1
PMid:14704851

92. Imai SI. "Clocks" in the NAD World: NAD as a metabolic oscillator for the regulation of metabolism and aging. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics. Aug 1;1804(8):1584-90. (2010)
DOI: 10.1016/j.bbapap.2009.10.024
PMid:19897060 PMCid:PMC2886185

93. Misiak M, Vergara Greeno R, Baptiste BA, Sykora P, Liu D, Cordonnier S, Fang EF, Croteau DL, Mattson MP, Bohr VA. DNA polymerase ß decrement triggers death of olfactory bulb cells and impairs olfaction in a mouse model of Alzheimer's disease. Aging cell. Feb;16(1):162-72. (2017)
DOI: 10.1111/acel.12541
PMid:27686631 PMCid:PMC5242308

94. Yoshino J, Baur JA, Imai SI. NAD+ intermediates: the biology and

therapeutic potential of NMN and NR. Cell metabolism. Mar 6;27(3):513-28. (2018)
DOI: 10.1016/j.cmet.2017.11.002
PMid:29249689 PMCid:PMC5842119

95. Aman Y, Qiu Y, Tao J, Fang EF. Therapeutic potential of boosting NAD+ in aging and age-related diseases. Translational Medicine of Aging. Jan 1;2:30-7. (2018)
DOI: 10.1016/j.tma.2018.08.003

96. Mitchell SJ, Bernier M, Aon MA, Cortassa S, Kim EY, Fang EF, Palacios HH, Ali A, Navas-Enamorado I, Di Francesco A, Kaiser TA. Nicotinamide improves aspects of healthspan, but not lifespan, in mice. Cell metabolism. Mar 6;27(3):667-76. (2018)
DOI: 10.1016/j.cmet.2018.02.001
PMid:29514072 PMCid:PMC5854409

97. Williams PA, Harder JM, Foxworth NE, Cochran KE, Philip VM, Porciatti V, Smithies O, John SW. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. Science. Feb 17;355(6326):756-60. (2017)
DOI: 10.1126/science.aal0092
PMid:28209901 PMCid:PMC5408298

98. Yoshino J, Mills KF, Yoon MJ, Imai SI. Nicotinamide mononucleotide, a key NAD+ intermediate, treats the pathophysiology of diet-and age-induced diabetes in mice. Cell metabolism. Oct 5;14(4):528-36. (2011)
DOI: 10.1016/j.cmet.2011.08.014
PMid:21982712 PMCid:PMC3204926

99. Peek CB, Affinati AH, Ramsey KM, Kuo HY, Yu W, Sena LA, Ilkayeva O, Marcheva B, Kobayashi Y, Omura C, Levine DC. Circadian clock NAD+ cycle drives mitochondrial oxidative metabolism in mice. Science. Nov 1;342(6158). (2013)
DOI: 10.1126/science.1243417
PMid:24051248 PMCid:PMC3963134

100. Stromsdorfer KL, Yamaguchi S, Yoon MJ, Moseley AC, Franczyk MP, Kelly SC, Qi N, Imai SI, Yoshino J. NAMPT-mediated NAD+ biosynthesis in adipocytes regulates adipose tissue function and multi-organ insulin sensitivity in mice. Cell reports. Aug 16;16(7):1851-60. (2016)
DOI: 10.1016/j.celrep.2016.07.027
PMid:27498863 PMCid:PMC5094180

101. Karamanlidis G, Lee CF, Garcia-Menendez L, Kolwicz Jr SC, Suthammarak W, Gong G, Sedensky MM, Morgan PG, Wang W, Tian R. Mitochondrial complex I deficiency increases protein acetylation and accelerates heart failure. Cell metabolism. Aug 6;18(2):239-50. (2013)
DOI: 10.1016/j.cmet.2013.07.002
PMid:23931755 PMCid:PMC3779647

102. Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, White JP, Teodoro JS, Wrann CD, Hubbard BP, Mercken EM. Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell. Dec 19;155(7):1624-38. (2013)
DOI: 10.1016/j.cell.2013.11.037
PMid:24360282 PMCid:PMC4076149

103. Guan Y, Wang SR, Huang XZ, Xie QH, Xu YY, Shang D, Hao CM. Nicotinamide Mononucleotide, an NAD+ Precursor, Rescues Age-Associated Susceptibility to AKI in a Sirtuin 1-Dependent Manner. Journal of the American Society of Nephrology. Aug 1;28(8):2337-52.

(2017)
DOI: 10.1681/ASN.2016040385
PMid:28246130 PMCid:PMC5533221

104. North BJ, Rosenberg MA, Jeganathan KB, Hafner AV, Michan S, Dai J, Baker DJ, Cen Y, Wu LE, Sauve AA, van Deursen JM. SIRT 2 induces the checkpoint kinase BubR1 to increase lifespan. The EMBO journal. Jul 1;33(13):1438-53. (2014)
DOI: 10.15252/embj.201386907
PMid:24825348 PMCid:PMC4194088

105. Lin JB, Kubota S, Ban N, Yoshida M, Santeford A, Sene A, Nakamura R, Zapata N, Kubota M, Tsubota K, Yoshino J. NAMPT-mediated NAD+ biosynthesis is essential for vision in mice. Cell reports. Sep 27;17(1):69-85. (2016)
DOI: 10.1016/j.celrep.2016.08.073
PMid:27681422 PMCid:PMC5104206

106. de Picciotto NE, Gano LB, Johnson LC, Martens CR, Sindler AL, Mills KF, Imai SI, Seals DR. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. Aging Cell. Jun;15(3):522-30. (2016)
DOI: 10.1111/acel.12461
PMid:26970090 PMCid:PMC4854911

107. Mills KF, Yoshida S, Stein LR, Grozio A, Kubota S, Sasaki Y, Redpath P, Migaud ME, Apte RS, Uchida K, Yoshino J. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. Cell metabolism. Dec 13;24(6):795-806. (2016)
DOI: 10.1016/j.cmet.2016.09.013
PMid:28068222 PMCid:PMC5668137

108. Fang EF, Lautrup S, Hou Y, Demarest TG, Croteau DL, Mattson MP, Bohr VA. NAD+ in aging: molecular mechanisms and translational implications. Trends in molecular medicine. Oct 1;23(10):899-916. (2017)
DOI: 10.1016/j.molmed.2017.08.001
PMid:28899755

109. Gulshan M, Yaku K, Okabe K, Mahmood A, Sasaki T, Yamamoto M, Hikosaka K, Usui I, Kitamura T, Tobe K, Nakagawa T. Overexpression of Nmnat3 efficiently increases NAD and NGD levels and ameliorates age-associated insulin resistance. Aging cell. Aug;17(4):e12798. (2018)
DOI: 10.1111/acel.12798
PMid:29901258 PMCid:PMC6052485

110. Caton PW, Kieswich J, Yaqoob MM, Holness MJ, Sugden MC. Nicotinamide mononucleotide protects against pro-inflammatory cytokine-mediated impairment of mouse islet function. Diabetologia. Dec 1;54(12):3083-92. (2011)
DOI: 10.1007/s00125-011-2288-0
PMid:21901281

111. Ramsey KM, Mills KF, Satoh A, Imai SI. Age-associated loss of Sirt1-mediated enhancement of glucose-stimulated insulin secretion in beta cell-specific Sirt1-overexpressing (BESTO) mice. Aging cell. Feb;7(1):78-88. (2008)
DOI: 10.1111/j.1474-9726.2007.00355.x
PMid:18005249 PMCid:PMC2238677

112. Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, Mitchell JR, Croteau DL, Bohr VA. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD+/SIRT1 reduction. Cell. May 8;157(4):882-96. (2014)
DOI: 10.1016/j.cell.2014.03.026

PMid:24813611 PMCid:PMC4625837

113. Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, Iser WB. NAD+ replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair. Cell metabolism. Oct 11;24(4):566-81. (2016)
DOI: 10.1016/j.cmet.2016.09.004
PMid:27732836 PMCid:PMC5777858

114. Fang EF, Bohr VA. NAD+: The convergence of DNA repair and mitophagy. Autophagy. Feb 1;13(2):442-3. (2017)
DOI: 10.1080/15548627.2016.1257467
PMid:27929719 PMCid:PMC5324847

115. Gallo CM, Smith DL, Smith JS. Nicotinamide clearance by Pnc1 directly regulates Sir2-mediated silencing and longevity. Molecular and cellular biology. Feb 1;24(3):1301-12. (2004)
DOI: 10.1128/MCB.24.3.1301-1312.2004
PMid:14729974 PMCid:PMC321434

116. Schmeisser K, Mansfeld J, Kuhlow D, Weimer S, Priebe S, Heiland I, Birringer M, Groth M, Segref A, Kanfi Y, Price NL. Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. Nature chemical biology. Nov;9(11):693-700. (2013)
DOI: 10.1038/nchembio.1352
PMid:24077178 PMCid:PMC4076143

117. van der Horst A, Schavemaker JM, Pellis-van Berkel W, Burgering BM. The Caenorhabditis elegans nicotinamidase PNC-1 enhances survival. Mechanisms of ageing and development. Apr 1;128(4):346-9. (2007)
DOI: 10.1016/j.mad.2007.01.004
PMid:17335870

118. Stein LR, Imai SI. Specific ablation of Nampt in adult neural stem cells recapitulates their functional defects during aging. The EMBO journal. Jun 17;33(12):1321-40. (2014)
DOI: 10.1002/embj.201386917

119. Yoon MJ, Yoshida M, Johnson S, Takikawa A, Usui I, Tobe K, Nakagawa T, Yoshino J, Imai SI. SIRT1-mediated eNAMPT secretion from adipose tissue regulates hypothalamic NAD+ and function in mice. Cell metabolism. May 5;21(5):706-17. (2015)
DOI: 10.1016/j.cmet.2015.04.002
PMid:25921090 PMCid:PMC4426056

120. Zhang R, Shen Y, Zhou L, Sangwung P, Fujioka H, Zhang L, Liao X. Short-term administration of nicotinamide mononucleotide preserves cardiac mitochondrial homeostasis and prevents heart failure. Journal of molecular and cellular cardiology. Nov 1;112:64-73. (2017)
DOI: 10.1016/j.yjmcc.2017.09.001
PMid:28882480 PMCid:PMC6257991

121. Imai SI, Guarente L. It takes two to tango: NAD+ and sirtuins in aging/longevity control. npj Aging and Mechanisms of Disease. Aug 18;2(1):1-6. (2016)
DOI: 10.1038/npjamd.2016.17
PMid:28721271 PMCid:PMC5514996

122. Kiss T, Balasubramanian P, Valcarcel-Ares MN, Tarantini S, Yabluchanskiy A, Csipo T, Lipecz A, Reglodi D, Zhang XA, Bari F, Farkas E. Nicotinamide mononucleotide (NMN) treatment attenuates oxidative stress and rescues angiogenic capacity in aged

cerebromicrovascular endothelial cells: a potential mechanism for the prevention of vascular cognitive impairment. GeroScience. Oct 1;41(5):619-30. (2019)
DOI: 10.1007/s11357-019-00074-2
PMid:31144244 PMCid:PMC6885080

123. Stein LR, Imai SI. Specific ablation of Nampt in adult neural stem cells recapitulates their functional defects during aging. The EMBO journal. Jun 17;33(12):1321-40. (2014)
DOI: 10.1002/embj.201386917

124. Long AN, Owens K, Schlappal AE, Kristian T, Fishman PS, Schuh RA. Effect of nicotinamide mononucleotide on brain mitochondrial respiratory deficits in an Alzheimer's disease-relevant murine model. BMC neurology. Dec;15(1):1-4. (2015)
DOI: 10.1186/s12883-015-0272-x
PMid:25884176 PMCid:PMC4358858

125. Wang X, Hu X, Yang Y, Takata T, Sakurai T. Nicotinamide mononucleotide protects against ß-amyloid oligomer-induced cognitive impairment and neuronal death. Brain research. Jul 15;1643:1-9. (2016)
DOI: 10.1016/j.brainres.2016.04.060
PMid:27130898

126. Yao Z, Yang W, Gao Z, Jia P. Nicotinamide mononucleotide inhibits JNK activation to reverse Alzheimer disease. Neuroscience letters. Apr 24;647:133-40. (2017)
DOI: 10.1016/j.neulet.2017.03.027
PMid:28330719

127. Yamamoto T, Byun J, Zhai P, Ikeda Y, Oka S, Sadoshima J. Nicotinamide mononucleotide, an intermediate of NAD+ synthesis, protects the heart from ischemia and reperfusion. PloS one. Jun 6;9(6):e98972. (2014)
DOI: 10.1371/journal.pone.0098972
PMid:24905194 PMCid:PMC4048236

128. Park JH, Long A, Owens K, Kristian T. Nicotinamide mononucleotide inhibits post-ischemic NAD+ degradation and dramatically ameliorates brain damage following global cerebral ischemia. Neurobiology of disease. Nov 1;95:102-10. (2016)
DOI: 10.1016/j.nbd.2016.07.018
PMid:27425894 PMCid:PMC5580241

129. Poljsak B, Milisav I. NAD+ as the link between oxidative stress, inflammation, caloric restriction, exercise, DNA repair, longevity, and health span. Rejuvenation research. Oct 1;19(5):406-13. (2016)
DOI: 10.1089/rej.2015.1767
PMid:26725653

130. Belenky P, Racette FG, Bogan KL, McClure JM, Smith JS, Brenner C. Nicotinamide riboside promotes Sir2 silencing and extends lifespan via Nrk and Urh1/Pnp1/Meu1 pathways to NAD+. Cell. May 4;129(3):473-84. (2007)
DOI: 10.1016/j.cell.2007.03.024
PMid:17482543

131. Lu SP, Kato M, Lin SJ. Assimilation of endogenous nicotinamide riboside is essential for calorie restriction-mediated life span extension in Saccharomyces cerevisiae. Journal of Biological Chemistry. Jun 19;284(25):17110-9. (2009)
DOI: 10.1074/jbc.M109.004010
PMid:19416965 PMCid:PMC2719349

132. Zhang H, Ryu D, Wu Y, Gariani K, Wang X, Luan P, D'Amico D, Ropelle ER,

Lutolf MP, Aebersold R, Schoonjans K. NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice. Science. Jun 17;352(6292):1436-43. (2016)
DOI: 10.1126/science.aaf2693
PMid:27127236

133. Tsang F, James C, Kato M, Myers V, Ilyas I, Tsang M, Lin SJ. Reduced Ssy1-Ptr3-Ssy5 (SPS) signaling extends replicative life span by enhancing NAD+ homeostasis in Saccharomyces cerevisiae. Journal of Biological Chemistry. May 15;290(20):12753-64. (2015)
DOI: 10.1074/jbc.M115.644534
PMid:25825491 PMCid:PMC4432292

134. Cantó C, Houtkooper RH, Pirinen E, Youn DY, Oosterveer MH, Cen Y, Fernandez-Marcos PJ, Yamamoto H, Andreux PA, Cettour-Rose P, Gademann K. The NAD+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. Cell metabolism. Jun 6;15(6):838-47. (2012)
DOI: 10.1016/j.cmet.2012.04.022
PMid:22682224 PMCid:PMC3616313

135. Xu W, Barrientos T, Mao L, Rockman HA, Sauve AA, Andrews NC. Lethal cardiomyopathy in mice lacking transferrin receptor in the heart. Cell reports. Oct 20;13(3):533-45. (2015)
DOI: 10.1016/j.celrep.2015.09.023
PMid:26456827 PMCid:PMC4618069

136. Trammell SA, Weidemann BJ, Chadda A, Yorek MS, Holmes A, Coppey LJ, Obrosov A, Kardon RH, Yorek MA, Brenner C. Nicotinamide riboside opposes type 2 diabetes and neuropathy in mice. Scientific reports. May 27;6:26933. (2016)
DOI: 10.1038/srep26933
PMid:27230286 PMCid:PMC4882590

137. Zhou CC, Yang X, Hua X, Liu J, Fan MB, Li GQ, Song J, Xu TY, Li ZY, Guan YF, Wang P. Hepatic NAD+ deficiency as a therapeutic target for non-alcoholic fatty liver disease in ageing. British journal of pharmacology. Aug 1;173(15):2352-68. (2016)
DOI: 10.1111/bph.13513
PMid:27174364 PMCid:PMC4945761

138. Ryu D, Zhang H, Ropelle ER, Sorrentino V, Mázala DA, Mouchiroud L, Marshall PL, Campbell MD, Ali AS, Knowels GM, Bellemin S. NAD+ repletion improves muscle function in muscular dystrophy and counters global PARylation. Science translational medicine. Oct 19;8(361):361ra139. (2016)
DOI: 10.1126/scitranslmed.aaf5504
PMid:27798264 PMCid:PMC5535761

139. Frederick DW, Loro E, Liu L, Davila Jr A, Chellappa K, Silverman IM, Quinn III WJ, Gosai SJ, Tichy ED, Davis JG, Mourkioti F. Loss of NAD homeostasis leads to progressive and reversible degeneration of skeletal muscle. Cell metabolism. Aug 9;24(2):269-82. (2016)
DOI: 10.1016/j.cmet.2016.07.005
PMid:27508874 PMCid:PMC4985182

140. Schöndorf DC, Ivanyuk D, Baden P, Sanchez-Martinez A, De Cicco S, Yu C, Giunta I, Schwarz LK, Di Napoli G, Panagiotakopoulou V, Nestel S. The NAD+ precursor nicotinamide riboside rescues mitochondrial defects and neuronal loss in iPSC and fly models of Parkinson's disease. Cell reports. Jun 5;23(10):2976-88. (2018)

DOI: 10.1016/j.celrep.2018.05.009
PMid:29874584

141. Gong B, Pan Y, Vempati P, Zhao W, Knable L, Ho L, Wang J, Sastre M, Ono K, Sauve AA, Pasinetti GM. Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-γ coactivator 1a regulated ß-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. Neurobiology of aging. Jun 1;34(6):1581-8. (2013)
DOI: 10.1016/j.neurobiolaging.-2012.12.005
PMid:23312803 PMCid:PMC3632303

142. Hou Y, Lautrup S, Cordonnier S, Wang Y, Croteau DL, Zavala E, Zhang Y, Moritoh K, O'Connell JF, Baptiste BA, Stevnsner TV. NAD+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. Proceedings of the National Academy of Sciences. Feb 20;115(8):E1876-85. (2018)
DOI: 10.1073/pnas.1718819115
PMid:29432159 PMCid:PMC5828618

143. Sorrentino V, Romani M, Mouchiroud L, Beck JS, Zhang H, D'Amico D, Moullan N, Potenza F, Schmid AW, Rietsch S, Counts SE. Enhancing mitochondrial proteostasis reduces amyloid-ß proteotoxicity. Nature. Dec;552(7684):-187-93. (2017)
DOI: 10.1038/nature25143
PMid:29211722 PMCid:PMC5730497

144. Trammell SA, Schmidt MS, Weidemann BJ, Redpath P, Jaksch F, Dellinger RW, Li Z, Abel ED, Migaud ME, Brenner C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nature communications. Oct 10;7:12948. (2016)
DOI: 10.1038/ncomms12948
PMid:27721479 PMCid:PMC5062546

145. Frederick DW, Davis JG, Dávila A, Agarwal B, Michan S, Puchowicz MA, Nakamaru-Ogiso E, Baur JA. Increasing NAD synthesis in muscle via nicotinamide phosphoribosyltransferase is not sufficient to promote oxidative metabolism. Journal of Biological Chemistry. Jan 16;290(3):1546-58. (2015)
DOI: 10.1074/jbc.M114.579565
PMid:25411251 PMCid:PMC4340401

146. Dellinger RW, Santos SR, Morris M, Evans M, Alminana D, Guarente L, Marcotulli E. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD+ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. npj Aging and Mechanisms of Disease. Nov 24;3(1):1-9. (2017)
DOI: 10.1038/s41514-017-0016-9
PMid:29184669 PMCid:PMC5701244

147. Martens CR, Denman BA, Mazzo MR, Armstrong ML, Reisdorph N, McQueen MB, Chonchol M, Seals DR. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. Nature communications. Mar 29;9(1):1-1. (2018)
DOI: 10.1038/s41467-018-03421-7
PMid:29599478 PMCid:PMC5876407

148. Wang YW, He SJ, Feng X, Cheng J, Luo YT, Tian L, Huang Q. Metformin: a review of its potential indications. Drug design, development and therapy.

11:2421. (2017)
DOI: 10.2147/DDDT.S141675
PMid:28860713 PMCid:PMC5574599

149. Glossmann HH, Lutz OM. Metformin and aging: a review. Gerontology. 65(6):581-90. (2019)
DOI: 10.1159/000502257
PMid:31522175

150. Podhorecka M, Ibanez B, Dmoszynska A. Metformin-its potential anti-cancer and anti-aging effects. Advances in Hygiene & Experimental Medicine/-Postepy Higieny i Medycyny Doswiadczalnej. Jan 1;71. (2017)
DOI: 10.5604/01.3001.0010.3801
PMid:28258677

151. Yerevanian A, Soukas AA. Metformin: mechanisms in human obesity and weight loss. Current obesity reports. Jun 1;8(2):156-64. (2019)
DOI: 10.1007/s13679-019-00335-3
PMid:30874963 PMCid:PMC6520185

152. Campbell JM, Stephenson MD, de Courten B, Chapman I, Bellman SM, Aromataris E. Metformin and Alzheimer's disease, dementia and cognitive impairment: a systematic review protocol. JBI Database of Systematic Reviews and Implementation Reports. Aug 1;15(8):2055-9. (2017)
DOI: 10.11124/JBISRIR-2017-003380
PMid:28800055

153. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metabolism. Jul 7;32(1):15-30. (2020)
DOI: 10.1016/j.cmet.2020.04.001
PMid:32333835 PMCid:PMC7347426

154. Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong J, Furlong TJ, Greenfield JR, Greenup LC, Kirkpatrick CM, Ray JE. Clinical pharmacokinetics of metformin. Clinical pharmacokinetics. Feb 1;50(2):81-98. (2011)
DOI: 10.2165/11534750-000000000-00000
PMid:21241070

155. Bridges HR, Sirviö VA, Agip AN, Hirst J. Molecular features of biguanides required for targeting of mitochondrial respiratory complex I and activation of AMP-kinase. BMC biology. Dec;14(1):1-1. (2016)
DOI: 10.1186/s12915-016-0287-9
PMid:27506389 PMCid:PMC4977651

156. De Haes W, Frooninckx L, Van Assche R, Smolders A, Depuydt G, Billen J, Braeckman BP, Schoofs L, Temmerman L. Metformin promotes lifespan through mitohormesis via the peroxiredoxin PRDX-2. Proceedings of the National Academy of Sciences. Jun 17;111(24):E2501-9. (2014)
DOI: 10.1073/pnas.1321776111
PMid:24889636 PMCid:PMC4066537

157. Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans healthspan via AMPK, LKB1, and SKN-1. PloS one. Jan 18;5(1):e8758. (2010)
DOI: 10.1371/journal.pone.0008758
PMid:20090912 PMCid:PMC2807458

158. Cameron AR, Logie L, Patel K, Erhardt S, Bacon S, Middleton P, Harthill J, Forteath C, Coats JT, Kerr C, Curry H. Metformin selectively targets redox control of complex I energy transduction. Redox biology. Apr 1;14:187-97. (2018)
DOI: 10.1016/j.redox.2017.08.018
PMid:28942196 PMCid:PMC5609876

159. Robb EL, Hall AR, Prime TA, Eaton S, Szibor M, Viscomi C, James AM, Murphy MP. Control of mitochondrial superoxide production by reverse electron transport at complex I. Journal of Biological Chemistry. Jun 22;293(25):9869-79. (2018)
DOI: 10.1074/jbc.RA118.003647
PMid:29743240 PMCid:PMC6016480

160. Hayden EC. Anti-ageing pill pushed as bona fide drug. Nature. Jun 18;522(7556). (2015)
DOI: 10.1038/522265a
PMid:26085249

161. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. Cell metabolism. Jun 14;23(6):1060-5. (2016)
DOI: 10.1016/j.cmet.2016.05.011
PMid:27304507 PMCid:PMC5943638

162. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M. Metformin improves healthspan and lifespan in mice. Nature communications. Jul 30;4(1):1-9. (2013)
DOI: 10.1038/ncomms3192
PMid:23900241 PMCid:PMC3736576

163. Cabreiro F, Au C, Leung KY, Vergara-Irigaray N, Cochemé HM, Noori T, Weinkove D, Schuster E, Greene ND, Gems D. Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism. Cell. Mar 28;153(1):228-39. (2013)
DOI: 10.1016/j.cell.2013.02.035
PMid:23540700 PMCid:PMC3898468

164. Rhee SG. Overview on peroxiredoxin. Molecules and cells. Jan 31;39(1):1. (2016)
DOI: 10.14348/molcells.2016.2368
PMid:26831451 PMCid:PMC4749868

165. Chen J, Ou Y, Li Y, Hu S, Shao LW, Liu Y. Metformin extends C. elegans lifespan through lysosomal pathway. Elife. Oct 13;6:e31268. (2017)
DOI: 10.7554/eLife.31268
PMid:29027899 PMCid:PMC5685485

166. Kim J, Lee HY, Ahn J, Hyun M, Lee I, Min KJ, You YJ. NHX-5, an endosomal Na+/H+ exchanger, is associated with metformin action. Journal of Biological Chemistry. Aug 26;291(35):18591-9. (2016)
DOI: 10.1074/jbc.C116.744037
PMid:27435670 PMCid:PMC5000102

167. Slack C, Foley A, Partridge L. Activation of AMPK by the putative dietary restriction mimetic metformin is insufficient to extend lifespan in Drosophila. PloS one. Oct 16;7(10):e47699. (2012)
DOI: 10.1371/journal.pone.0047699
PMid:23077661 PMCid:PMC3473082

168. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M. Metformin improves healthspan and lifespan in mice. Nature communications. Jul 30;4(1):1-9. (2013)
DOI: 10.1038/ncomms3192
PMid:23900241 PMCid:PMC3736576

169. Strong R, Miller RA, Antebi A, Astle CM, Bogue M, Denzel MS, Fernandez E, Flurkey K, Hamilton KL, Lamming DW, Javors MA. Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an a-glucosidase inhibitor or a Nrf2-inducer. Aging cell. Oct;15(5):872-84. (2016)

DOI: 10.1111/acel.12496
PMid:27312235 PMCid:PMC5013015

170. Anisimov VN. Metformin for aging and cancer prevention. Aging (Albany NY). Nov;2(11):760. (2010)
DOI: 10.18632/aging.100230
PMid:21084729 PMCid:PMC3006019

171. Anisimov VN, Berstein LM, Popovich IG, Zabezhinski MA, Egormin PA, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Kovalenko IG, Poroshina TE. If started early in life, metformin treatment increases life span and postpones tumors in female SHR mice. Aging (Albany NY). Feb;3(2):148. (2011)
DOI: 10.18632/aging.100273
PMid:21386129 PMCid:PMC3082009

172. Kalender A, Selvaraj A, Kim SY, Gulati P, Brûlé S, Viollet B, Kemp BE, Bardeesy N, Dennis P, Schlager JJ, Marette A. Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. Cell metabolism. May 5;11(5):390-401. (2010)
DOI: 10.1016/j.cmet.2010.03.014
PMid:20444419 PMCid:PMC3081779

173. Martel RR, Klicius J, Galet S. Inhibition of the immune response by rapamycin, a new antifungal antibiotic. Canadian journal of physiology and pharmacology. Feb 1;55(1):48-51. (1977)
DOI: 10.1139/y77-007
PMid:843990

174. Vezina C, Kudelski A, Sehgal SN. Rapamycin (AY-22, 989), a new antifungal antibiotic. The Journal of antibiotics. 28(10):721-6. (1975)
DOI: 10.7164/antibiotics.28.721
PMid:1102508

175. Sehgal SN, Baker H, Vezina C. Rapamycin (AY-22, 989), a new antifungal antibiotic. The Journal of antibiotics. 28(10):727-32. (1975)
DOI: 10.7164/antibiotics.28.727
PMid:1102509

176. Chung J, Kuo CJ, Crabtree GR, Blenis J. Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. Cell. Jun 26;69(7):1227-36. (1992)
DOI: 10.1016/0092-8674(92)90643-Q

177. Brown EJ, Albers MW, Shin TB, Keith CT, Lane WS, Schreiber SL. A mammalian protein targeted by G1-arresting rapamycin-receptor complex. Nature. Jun 30;369(6483):756-8. (1994)
DOI: 10.1038/369756a0
PMid:8008069

178. Sabatini DM, Erdjument-Bromage H, Lui M, Tempst P, Snyder SH. RAFT1: a mammalian protein that binds to FKBP12 in a rapamycin-dependent fashion and is homologous to yeast TORs. Cell. Jul 15;78(1):35-43. (1994)
DOI: 10.1016/0092-8674(94)90570-3

179. Sabers CJ, Martin MM, Brunn GJ, Williams JM, Dumont FJ, Wiederrecht G, Abraham RT. Isolation of a protein target of the FKBP12-rapamycin complex in mammalian cells. Journal of Biological Chemistry. Jan 13;270(2):815-22. (1995)
DOI: 10.1074/jbc.270.2.815
PMid:7822316

180. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. Apr 13;149(2):274-93. (2012)
DOI: 10.1016/j.cell.2012.03.017
PMid:22500797 PMCid:PMC3331679

181. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. Mar 9;168(6):960-76. (2017)
DOI: 10.1016/j.cell.2017.02.004
PMid:28283069 PMCid:PMC5394987

182. Anisimov VN, Zabezhinski MA, Popovich IG, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Rosenfeld SV, Blagosklonny MV. Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice. Cell cycle. Dec 15;10(24):4230-6. (2011)
DOI: 10.4161/cc.10.24.18486
PMid:22107964

183. Astrinidis A, Cash TP, Hunter DS, Walker CL, Chernoff J, Henske EP. Tuberin, the tuberous sclerosis complex 2 tumor suppressor gene product, regulates Rho activation, cell adhesion and migration. Oncogene. Dec;21(55):-8470-6. (2002)
DOI: 10.1038/sj.onc.1205962
PMid:12466966

184. Inoki K, Li Y, Zhu T, Wu J, Guan KL. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nature cell biology. Sep;4(9):648-57. (2002)
DOI: 10.1038/ncb839
PMid:12172553

185. Bjedov I, Toivonen JM, Kerr F, Slack C, Jacobson J, Foley A, Partridge L. Mechanisms of life span extension by rapamycin in the fruit fly Drosophila melanogaster. Cell metabolism. Jan 6;11(1):35-46. (2010)
DOI: 10.1016/j.cmet.2009.11.010
PMid:20074526 PMCid:PMC2824086

186. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. nature. Jul;460(7253):392-5. (2009)
DOI: 10.1038/nature08221
PMid:19587680 PMCid:PMC2786175

187. Medvedik O, Lamming DW, Kim KD, Sinclair DA. MSN2 and MSN4 link calorie restriction and TOR to sirtuin-mediated lifespan extension in Saccharomyces cerevisiae. PLoS Biol. Oct 2;5(10):e261. (2007)
DOI: 10.1371/journal.pbio.0050261
PMid:17914901 PMCid:PMC1994990

188. Blagosklonny MV. Linking calorie restriction to longevity through sirtuins and autophagy: any role for TOR. 1, 12 (2010)
DOI: 10.1038/cddis.2009.17
PMid:21364614 PMCid:PMC3032506

189. Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, De Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. The Journals of Gerontology: Series A. Feb 1;66(2):191-201. (2011)
DOI: 10.1093/gerona/glq178
PMid:20974732 PMCid:PMC3021372

190. Powers RW, Kaeberlein M, Caldwell SD, Kennedy BK, Fields S. Extension of chronological life span in yeast by decreased TOR pathway signaling. Genes & development. Jan 15;20(2):174-84. (2006)
DOI: 10.1101/gad.1381406
PMid:16418483 PMCid:PMC1356109

191. Robida-Stubbs S, Glover-Cutter K,

Lamming DW, Mizunuma M, Narasimhan SD, Neumann-Haefelin E, Sabatini DM, Blackwell TK. TOR signaling and rapamycin influence longevity by regulating SKN-1/Nrf and DAF-16/FoxO. Cell metabolism. May 2;15(5):713-24. (2012)
DOI: 10.1016/j.cmet.2012.04.007
PMid:22560223 PMCid:PMC3348514

192. Antikainen H, Driscoll M, Haspel G, Dobrowolski R. TOR-mediated regulation of metabolism in aging. Aging cell. Dec;16(6):1219-33. (2017)
DOI: 10.1111/acel.12689
PMid:28971552 PMCid:PMC5676073

193. Pan H, Finkel T. Key proteins and pathways that regulate lifespan. Journal of Biological Chemistry. Apr 21;292(16):6452-60. (2017)
DOI: 10.1074/jbc.R116.771915
PMid:28264931 PMCid:PMC5399099

194. Johnson SC, Yanos ME, Kayser EB, Quintana A, Sangesland M, Castanza A, Uhde L, Hui J, Wall VZ, Gagnidze A, Oh K. mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome. Science. Dec 20;342(6165):1524-8. (2013)
DOI: 10.1126/science.1244360
PMid:24231806 PMCid:PMC4055856

195. Chen C, Liu Y, Liu Y, Zheng P. mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. Science signaling. Nov 24;2(98):ra75. (2009)
DOI: 10.1126/scisignal.2000559
PMid:19934433 PMCid:PMC4020596

196. Nakatani Y, Yaguchi Y, Komura T, Nakadai M, Terao K, Kage-Nakadai E, Nishikawa Y. Sesamin extends lifespan through pathways related to dietary restriction in Caenorhabditis elegans. European journal of nutrition. Apr 1;57(3):1137-46. (2018)
DOI: 10.1007/s00394-017-1396-0
PMid:28239780

197. Sadowska-Bartosz I, Bartosz G. Effect of antioxidants supplementation on aging and longevity. BioMed Research International. 14; 1-17, (2014)
DOI: 10.1155/2014/404680
PMid:24783202 PMCid:PMC3982418

198. Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond M, Coskun PE, Ladiges W, Wolf N, Van Remmen H, Wallace DC. Extension of murine life span by overexpression of catalase targeted to mitochondria. science. Jun 24;308(5730):1909-11. (2005)
DOI: 10.1126/science.1106653
PMid:15879174

199. Rafique R, Schapira AH, Cooper JM. Mitochondrial respiratory chain dysfunction in ageing; influence of vitamin E deficiency. Free Radical Research. Feb 1;38(2):157-65. (2004)
DOI: 10.1080/10715760310001643311
PMid:15104209

200. Khavinson VK, Izmaylov DM, Obukhova LK, Malinin VV. Effect of epitalon on the lifespan increase in Drosophila melanogaster. Mechanisms of ageing and development. Dec 1;120(1-3):141-9. (2000)
DOI: 10.1016/S0047-6374(00)00217-7

201. Anisimov VN, Khavinson VK, Popovich IG, Zabezhinski MA, Alimova IN, Rosenfeld SV, Zavarzina NY, Semenchenko AV, Yashin AI. Effect of Epitalon on biomarkers of aging, life span and spontaneous tumor incidence

in female Swiss-derived SHR mice. Biogerontology. Aug 1;4(4):193-202. (2003)
DOI: 10.1023/A:1025114230714
PMid:14501183

202. Khavinson V. Peptides and Ageing. Neuro endocrinology letters. 23:11. (2002)

203. VKh K. Peptides and Ageing. Neuro Endocrinology Letters. Jan 1;23:11-44. (2002)

204. Hipkiss AR. Aging, proteotoxicity, mitochondria, glycation, NAD+ and carnosine: possible inter-relationships and resolution of the oxygen paradox. Frontiers in aging neuroscience. Mar 18;2:10. (2010)
DOI: 10.3389/fnagi.2010.00010
PMid:20552048 PMCid:PMC2874395

205. Aldini G, Facino RM, Beretta G, Carini M. Carnosine and related dipeptides as quenchers of reactive carbonyl species: from structural studies to therapeutic perspectives. Biofactors. Jan 1;24(1-4):77-87. (2005)
DOI: 10.1002/biof.5520240109
PMid:16403966

206. Boldyrev AA, Severin SE. The histidine-containing dipeptides, carnosine and anserine: distribution, properties and biological significance. Advances in enzyme regulation. Jan 1;30:175-88. (1990)
DOI: 10.1016/0065-2571(90)90017-V

207. Quinn PJ, Boldyrev AA, Formazuyk VE. Carnosine: its properties, functions and potential therapeutic applications. Molecular aspects of Medicine. Jan 1;13(5):379-444. (1992)
DOI: 10.1016/0098-2997(92)90006-L

208. Rashid I, van Reyk DM, Davies MJ. Carnosine and its constituents inhibit glycation of low-density lipoproteins that promotes foam cell formation *in vitro*. FEBS letters. Mar 6;581(5):1067-70. (2007)
DOI: 10.1016/j.febslet.2007.01.082
PMid:17316626

209. Babizhayev MA, Yegorov YE. Telomere attrition in lens epithelial cells-a target for N-acetylcarnosine therapy. cancer. 53:57. (2010)
DOI: 10.2741/3655
PMid:20515735

210. Dobrota D, Fedorova T, Stvolinsky S, Babusikova E, Likavcanova K, Drgova A, Strapkova A, Boldyrev A. Carnosine protects the brain of rats and Mongolian gerbils against ischemic injury: after-stroke-effect. Neurochemical research. 1;30(10):1283-8. (2005)
DOI: 10.1007/s11064-005-8799-7
PMid:16341589

211. Boldyrev A, Abe H, Stvolinsky S, Tyulina O. Effects of carnosine and related compounds on generation of free oxygen species: a comparative study. Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology. Nov 1;112(3):481-5. (1995)
DOI: 10.1016/0305-0491(95)00084-4

212. Boldyrev A, Song R, Lawrence D, Carpenter DO. Carnosine protects against excitotoxic cell death independently of effects on reactive oxygen species. Neuroscience. Sep 1;94(2):571-7. (1999)
DOI: 10.1016/S0306-4522(99)00273-0

213. Boldyrev AA, Stvolinsky SL, Tyulina OV, Koshelev VB, Hori N, Carpenter DO.

Biochemical and physiological evidence that carnosine is an endogenous neuroprotector against free radicals. Cellular and molecular neurobiology. Apr 1;17(2):259-71. (1997)
DOI: 10.1023/A:1026374114314
PMid:9140702

214. Shao L, Li QH, Tan Z. L-carnosine reduces telomere damage and shortening rate in cultured normal fibroblasts. Biochemical and biophysical research communications. Nov 12;324(2):931-6. (2004)
DOI: 10.1016/j.bbrc.2004.09.136
PMid:15474517

215. Corona C, Frazzini V, Silvestri E, Lattanzio R, La Sorda R, Piantelli M, Canzoniero LM, Ciavardelli D, Rizzarelli E, Sensi SL. Effects of dietary supplementation of carnosine on mitochondrial dysfunction, amyloid pathology, and cognitive deficits in 3xTg-AD mice. PloS one. Mar 15;6(3):e17971. (2011)
DOI: 10.1371/journal.pone.0017971
PMid:21423579 PMCid:PMC3058055

216. McFarland GA, Holliday R. Retardation of the senescence of cultured human diploid fibroblasts by carnosine. Experimental cell research. Jun 1;212(2):167-75. (1994)
DOI: 10.1006/excr.1994.1132
PMid:8187813

217. Wang AM, Ma C, Xie ZH, Shen F. Use of carnosine as a natural anti-senescence drug for human beings. Biochemistry C/C Of Biokhimiia. Jul 1;65(7):869-71. (2000)

218. Hipkiss AR, Brownson C. Carnosine reacts with protein carbonyl groups: another possible role for the anti-ageing peptide? Biogerontology. Sep 1;1(3):217-23. (2000)

219. Stvolinsky S, Antipin M, Meguro K, Sato T, Abe H, Boldyrev A. Effect of carnosine and its Trolox-modified derivatives on life span of Drosophila melanogaster. Rejuvenation Research. Aug 1;13(4):453-7. (2010)
DOI: 10.1089/rej.2009.1010
PMid:20681748

220. Maher PA, Schubert DR. Metabolic links between diabetes and Alzheimer's disease. Expert review of neuro-therapeutics. May 1;9(5):617-30. (2009)
DOI: 10.1586/ern.09.18
PMid:19402773

221. Hipkiss AR. Carnosine, diabetes and Alzheimer's disease. Expert review of neurotherapeutics. May 1;9(5):583-5. (2009)
DOI: 10.1586/ern.09.32
PMid:19402768

222. Hipkiss AR. Error-protein metabolism and ageing. Biogerontology. Aug 1;10(4):523. (2009)
DOI: 10.1007/s10522-008-9188-9
PMid:18923917

223. Hipkiss AR, Chana H. Carnosine protects proteins against methylglyoxal-mediated modifications. Biochemical and biophysical research communications. Jul 9;248(1):28-32. (1998)
DOI: 10.1006/bbrc.1998.8806
PMid:9675080

224. Hipkiss AR. Could carnosine or related structures suppress Alzheimer's disease? Journal of Alzheimer's Disease. Jan 1;11(2):229-40. (2007)
DOI: 10.3233/JAD-2007-11210

PMid:17522447

225. Hipkiss AR. Energy metabolism, altered proteins, sirtuins and ageing: converging mechanisms? Biogerontology. Feb 1;9(1):49-55. (2008)
DOI: 10.1007/s10522-007-9110-x
PMid:17929190 PMCid:PMC2174522

226. Timmers S, Auwerx J, Schrauwen P. The journey of resveratrol from yeast to human. Aging (Albany NY). Mar;4(3):146. (2012)
DOI: 10.18632/aging.100445
PMid:22436213 PMCid:PMC3348475

227. Schrauwen P, Auwerx J, Timmers S. The journey of resveratrol from yeast to human. Aging. Mar 12;4(3):146-58. (2012)
DOI: 10.18632/aging.100445
PMid:22436213 PMCid:PMC3348475

228. Salehi B, Mishra AP, Nigam M, Sener B, Kilic M, Sharifi-Rad M, Fokou PV, Martins N, Sharifi-Rad J. Resveratrol: A double-edged sword in health benefits. Biomedicines. Sep;6(3):91. (2018) DOI: 10.3390/biomedicines6030091
PMid:30205595 PMCid:PMC6164842

229. Baron S, Bedarida T, Cottart CH, Vibert F, Vessieres E, Ayer A, Henrion D, Hommeril B, Paul JL, Renault G, Saubamea B. Dual effects of resveratrol on arterial damage induced by insulin resistance in aged mice. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. Mar 1;69(3):260-9. (2014)
DOI: 10.1093/gerona/glt081
PMid:23793060

230. Rege SD, Geetha T, Griffin GD, Broderick TL, Babu JR. Neuroprotective effects of resveratrol in Alzheimer disease pathology. Frontiers in aging neuroscience. Sep 11;6:218. (2014)
DOI: 10.3389/fnagi.2014.00218
PMid:25309423 PMCid:PMC4161050

231. Shen LR, Parnell LD, Ordovas JM, Lai CQ. Curcumin and aging. Biofactors. Jan;39(1):133-40. (2013)
DOI: 10.1002/biof.1086
PMid:23325575

232. Bagheri H, Ghasemi F, Barreto GE, Rafiee R, Sathyapalan T, Sahebkar A. Effects of curcumin on mitochondria in neurodegenerative diseases. BioFactors. Jan;46(1):5-20. (2020)
DOI: 10.1002/biof.1566
PMid:31580521

233. Kitani K, Osawa T, Yokozawa T. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. Biogerontology. Oct 1;8(5):567-73. (2007)
DOI: 10.1007/s10522-007-9100-z
PMid:17516143

234. Plummer SM, Holloway KA, Manson MM, Munks RJ, Kaptein A, Farrow S, Howells L. Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. Oncogene. Oct;18(44):6013-20. (1999)
DOI: 10.1038/sj.onc.1202980
PMid:10557090

235. Beevers CS, Li F, Liu L, Huang S. Curcumin inhibits the mammalian target of rapamycin-mediated signaling pathways in cancer cells. International journal of cancer. Aug 15;119(4):757-64. (2006)
DOI: 10.1002/ijc.21932
PMid:16550606

236. Pu Y, Zhang H, Wang P, Zhao Y, Li Q, Wei X, Cui Y, Sun J, Shang Q, Liu D, Zhu Z. Dietary curcumin ameliorates aging-related cerebrovascular dysfunction through the AMPK/uncoupling protein 2 pathway. Cellular Physiology and Biochemistry. 32(5):1167-77. (2013)
DOI: 10.1159/000354516
PMid:24335167

237. Hewlings SJ, Kalman DS. Curcumin: a review of its' effects on human health. Foods. Oct;6(10):92. (2017)
DOI: 10.3390/foods6100092
PMid:29065496 PMCid:PMC5664031

238. Lee KS, Lee BS, Semnani S, Avanesian A, Um CY, Jeon HJ, Seong KM, Yu K, Min KJ, Jafari M. Curcumin extends life span, improves health span, and modulates the expression of age-associated aging genes in Drosophila melanogaster. Rejuvenation Research. Oct 1;13(5):561-70. (2010)
DOI: 10.1089/rej.2010.1031
PMid:20645870

239. Cañuelo A, Gilbert-López B, Pacheco-Liñán P, Martínez-Lara E, Siles E, Miranda-Vizuete A. Tyrosol, a main phenol present in extra virgin olive oil, increases lifespan and stress resistance in Caenorhabditis elegans. Mechanisms of ageing and development. Aug 1;133(8):563-74. (2012)
DOI: 10.1016/j.mad.2012.07.004
PMid:22824366

240. Maher P. Modulation of multiple pathways involved in the maintenance of neuronal function during aging by fisetin. Genes & nutrition. Dec 1;4(4):297. (2009)
DOI: 10.1007/s12263-009-0142-5
PMid:19756810 PMCid:PMC2775892

241. Currais A, Farrokhi C, Dargusch R, Armando A, Quehenberger O, Schubert D, Maher P. Fisetin reduces the impact of aging on behavior and physiology in the rapidly aging SAMP8 mouse. The journals of gerontology: series A. Mar 2;73(3):299-307. (2018)
DOI: 10.1093/gerona/glx104
PMid:28575152 PMCid:PMC5861950

242. Singh S, Singh AK, Garg G, Rizvi SI. Fisetin as a caloric restriction mimetic protects rat brain against aging induced oxidative stress, apoptosis and neurodegeneration. Life sciences. Jan 15;193:171-9. (2018)
DOI: 10.1016/j.lfs.2017.11.004
PMid:29122553

243. Zhu Y, Doornebal EJ, Pirtskhalava T, Giorgadze N, Wentworth M, Fuhrmann-Stroissnigg H, Niedernhofer LJ, Robbins PD, Tchkonia T, Kirkland JL. New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. Aging (Albany NY). Mar;9(3):955. (2017)
DOI: 10.18632/aging.101202
PMid:28273655 PMCid:PMC5391241

244. Li X, Wang H, Gao Y, Li L, Tang C, Wen G, Zhou Y, Zhou M, Mao L, Fan Y. Protective effects of quercetin on mitochondrial biogenesis in experimental traumatic brain injury via the Nrf2 signaling pathway. PLoS One. Oct 25;11(10):e0164237. (2016)
DOI: 10.1371/journal.pone.0164237
PMid:27780244 PMCid:PMC5079551

245. Singh A, Naidu PS, Kulkarni SK. Reversal of aging and chronic ethanol-induced cognitive dysfunction by quercetin a bioflavonoid. Free radical research. 2003 1;37(11):1245-52. (Jan)
DOI: 10.1080/10715760310001616014

PMid:14703737

246. Stefek M, Karasu C. Eye lens in aging and diabetes: effect of quercetin. Rejuvenation Research. Oct 1;14(5):525-34. (2011)
DOI: 10.1089/rej.2011.1170
PMid:21978083

247. Geng L, Liu Z, Zhang W, Li W, Wu Z, Wang W, Ren R, Su Y, Wang P, Sun L, Ju Z. Chemical screen identifies a geroprotective role of quercetin in premature aging. Protein & cell. Jun 1;10(6):417-35. (2019)
DOI: 10.1007/s13238-018-0567-y
PMid:30069858 PMCid:PMC6538594

248. Liu J, Yu H, Ning X. Effect of quercetin on chronic enhancement of spatial learning and memory of mice. Science in China Series C: Life Sciences. Dec 1;49(6):583-90. (2006)
DOI: 10.1007/s11427-006-2037-7
PMid:17312997

249. Sun Y, Yang T, K Leak R, Chen J, Zhang F. Preventive and protective roles of dietary Nrf2 activators against central nervous system diseases. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). Apr 1;16(3):326-38. (2017)
DOI: 10.2174/1871527316666-170102120211
PMid:28042770 PMCid:PMC5494269

250. Rojo de la Vega M, Zhang DD, Wondrak GT. Topical bixin confers NRF2-dependent protection against photo-damage and hair graying in mouse skin. Frontiers in pharmacology. Mar 27;9:287. (2018)
DOI: 10.3389/fphar.2018.00287
PMid:29636694 PMCid:PMC5880955

251. Zhang M, Wang S, Mao L, Leak RK, Shi Y, Zhang W, Hu X, Sun B, Cao G, Gao Y, Xu Y. Omega-3 fatty acids protect the brain against ischemic injury by activating Nrf2 and upregulating heme oxygenase 1. Journal of Neuroscience. Jan 29;34(5):1903-15. (2014)
DOI: 10.1523/JNEUROSCI.4043-13.2014
PMid:24478369 PMCid:PMC3905150

252. Carney JM, Starke-Reed PE, Oliver CN, Landum RW, Cheng MS, Wu JF, Floyd RA. Reversal of age-related increase in brain protein oxidation, decrease in enzyme activity, and loss in temporal and spatial memory by chronic administration of the spin-trapping compound N-tert-butyl-alpha-phenyl-nitrone. Proceedings of the National Academy of Sciences. May 1;88(9):3633-6. (1991)
DOI: 10.1073/pnas.88.9.3633
PMid:1673789 PMCid:PMC51506

253. Shetty RA, Forster MJ, Sumien N. Coenzyme Q 10 supplementation reverses age-related impairments in spatial learning and lowers protein oxidation. Age. Oct 1;35(5):1821-34. (2013)
DOI: 10.1007/s11357-012-9484-9
PMid:23138632 PMCid:PMC3776107

254. Pacheco LM, Gomez LA, Dias J, Ziebarth NM, Howard GA, Schiller PC. Progerin expression disrupts critical adult stem cell functions involved in tissue repair. Aging (Albany NY). Dec;6(12):1049. (2014)
DOI: 10.18632/aging.100709
PMid:25567453 PMCid:PMC4298365

255. Rosengardten Y, McKenna T, Grochová D, Eriksson M. Stem cell depletion in Hutchinson-Gilford progeria syndrome.

Aging cell. Dec;10(6):1011-20. (2011)
DOI: 10.1111/j.1474-9726.2011.00743.x
PMid:21902803

256. Scaffidi P, Misteli T. Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. Nature cell biology. Apr;10(4):452-9. (2008)
DOI: 10.1038/ncb1708
PMid:18311132 PMCid:PMC2396576

257. Liu GH, Barkho BZ, Ruiz S, Diep D, Qu J, Yang SL, Panopoulos AD, Suzuki K, Kurian L, Walsh C, Thompson J. Recapitulation of premature ageing with iPSCs from Hutchinson-Gilford progeria syndrome. Nature. Apr;472(7342):221-5. (2011)
DOI: 10.1038/nature09879
PMid:21346760 PMCid:PMC3088088

258. Liu B, Ghosh S, Yang X, Zheng H, Liu X, Wang Z, Jin G, Zheng B, Kennedy BK, Suh Y, Kaeberlein M. Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in laminopathy-based progeria. Cell metabolism. Dec 5;16(6):738-50. (2012)
DOI: 10.1016/j.cmet.2012.11.007
PMid:23217256

259. Zhang J, Lian Q, Zhu G, Zhou F, Sui L, Tan C, Mutalif RA, Navasankari R, Zhang Y, Tse HF, Stewart CL. A human iPSC model of Hutchinson Gilford Progeria reveals vascular smooth muscle and mesenchymal stem cell defects. Cell stem cell. Jan 7;8(1):31-45. (2011)
DOI: 10.1016/j.stem.2010.12.002
PMid:21185252

260. Kubben N, Zhang W, Wang L, Voss TC, Yang J, Qu J, Liu GH, Misteli T. Repression of the antioxidant NRF2 pathway in premature aging. Cell. Jun 2;165(6):1361-74 (2016)
DOI: 10.1016/j.cell.2016.05.017
PMid:27259148 PMCid:PMC4893198

261. Lee KP, Simpson SJ, Clissold FJ, Brooks R, Ballard JW, Taylor PW, Soran N, Raubenheimer D. Lifespan and reproduction in Drosophila: new insights from nutritional geometry. Proceedings of the National Academy of Sciences. Feb 19;105(7):2498-503. (2008)
DOI: 10.1073/pnas.0710787105
PMid:18268352 PMCid:PMC2268165

262. Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen K, Wu LE, Cogger VC, Warren A, Huang X, Pichaud N, Melvin RG, Gokarn R. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. Cell metabolism. Mar 4;19(3):418-30. (2014)
DOI: 10.1016/j.cmet.2014.02.009
PMid:24606899 PMCid:PMC5087279

263. Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen K, Wu LE, Cogger VC, Warren A, Huang X, Pichaud N, Melvin RG, Gokarn R. Erratum: The Ratio of Macronutrients, Not Caloric Intake, Dictates Cardiometabolic Health, Aging, and Longevity in Ad Libitum-Fed Mice (Cell Metabolism (2014) 19 (3)(418-430). Cell Metabolism. Mar 3;31(3). (2020)
DOI: 10.1016/j.cmet.2014.02.009
PMid:24606899 PMCid:PMC5087279

264. Brown-Borg HM. Reduced growth hormone signaling and methionine restriction: interventions that improve metabolic health and extend life span. Annals of the New York Academy of

Sciences. Jan;1363:40. (2016)
DOI: 10.1111/nyas.12971
PMid:26645136 PMCid:PMC6472264

265. Brown-Borg HM, Rakoczy SG, Wonderlich JA, Rojanathammanee L, Kopchick JJ, Armstrong V, Raasakka D. Growth hormone signaling is necessary for lifespan extension by dietary methionine. Aging cell. Dec;13(6):1019-27. (2014)
DOI: 10.1111/acel.12269
PMid:25234161 PMCid:PMC4244257

266. Johnson JE, Johnson FB. Methionine restriction activates the retrograde response and confers both stress tolerance and lifespan extension to yeast, mouse and human cells. PloS one. May 15;9(5):e97729. (2014)
DOI: 10.1371/journal.pone.0097729
PMid:24830393 PMCid:PMC4022668

267. Kozieł R, Ruckenstuhl C, Albertini E, Neuhaus M, Netzberger C, Bust M, Madeo F, Wiesner RJ, Jansen-Dürr P. Methionine restriction slows down senescence in human diploid fibroblasts. Aging cell. Dec;13(6):1038-48. (2014)
DOI: 10.1111/acel.12266
PMid:25273919 PMCid:PMC4326930

268. Lee BC, Kaya A, Ma S, Kim G, Gerashchenko MV, Yim SH, Hu Z, Harshman LG, Gladyshev VN. Methionine restriction extends lifespan of Drosophila melanogaster under conditions of low amino-acid status. Nature communications. Apr 7;5(1):1-2 (2014)
DOI: 10.1038/ncomms4592
PMid:24710037 PMCid:PMC4350766

269. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. Aging cell. Jun;4(3):119-25. (2005)
DOI: 10.1111/j.1474-9726.2005.00152.x
PMid:15924568 PMCid:PMC7159399

270. Ruckenstuhl C, Netzberger C, Entfellner I, Carmona-Gutierrez D, Kickenweiz T, Stekovic S, Gleixner C, Schmid C, Klug L, Sorgo AG, Eisenberg T. Lifespan extension by methionine restriction requires autophagy-dependent vacuolar acidification. PLoS Genet. May 1;10(5):e1004347. (2014)
DOI: 10.1371/journal.pgen.1004347
PMid:24785424 PMCid:PMC4006742

271. Richie Jr JP, Leutzinger Y, Parthasarathy S, Maixoy V, Orentreich N, Zimmerman JA. Methionine restriction increases blood glutathione and longevity in F344 rats. The FASEB Journal. Dec;8(15):1302-7. (1994)
DOI: 10.1096/fasebj.8.15.8001743
PMid:8001743

272. Sun L, Sadighi Akha AA, Miller RA, Harper JM. Life-span extension in mice by preweaning food restriction and by methionine restriction in middle age. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. Jul 1;64(7):711-22. (2009)
DOI: 10.1093/gerona/glp051
PMid:19414512 PMCid:PMC2691799

273. Lees EK, Król E, Grant L, Shearer K, Wyse C, Moncur E, Bykowska AS, Mody N, Gettys TW, Delibegovic M. Methionine restriction restores a

younger metabolic phenotype in adult mice with alterations in fibroblast growth factor 21. Aging cell. Oct;13(5):817-27. (2014)
DOI: 10.1111/acel.12238
PMid:24935677 PMCid:PMC4331744

274. Caro P, Gomez J, Sanchez I, Naudi A, Ayala V, López-Torres M, Pamplona R, Barja G. Forty percent methionine restriction decreases mitochondrial oxygen radical production and leak at complex I during forward electron flow and lowers oxidative damage to proteins and mitochondrial DNA in rat kidney and brain mitochondria. Rejuvenation research. Dec 1;12(6):421-34. (2009)
DOI: 10.1089/rej.2009.0902
PMid:20041736

275. Ables GP, Perrone CE, Orentreich D, Orentreich N. Methionine-restricted C57BL/6J mice are resistant to diet-induced obesity and insulin resistance but have low bone density. PloS one. Dec 7;7(12):e51357. (2012)
DOI: 10.1371/journal.pone.0051357
PMid:23236485 PMCid:PMC3518083

276. Benavides GA, Squadrito GL, Mills RW, Patel HD, Isbell TS, Patel RP, Darley-Usmar VM, Doeller JE, Kraus DW. Hydrogen sulfide mediates the vasoactivity of garlic. Proceedings of the National Academy of Sciences. Nov 13;104(46):17977-82. (2007)
DOI: 10.1073/pnas.0705710104
PMid:17951430 PMCid:PMC2084282

277. Kashfi K. Anti-cancer activity of new designer hydrogen sulfide-donating hybrids. Antioxidants & redox signaling. Feb 10;20(5):831-46. (2014)
DOI: 10.1089/ars.2013.5308
PMid:23581880 PMCid:PMC3910473

278. Pei Y, Wu B, Cao Q, Wu L, Yang G. Hydrogen sulfide mediates the anti-survival effect of sulforaphane on human prostate cancer cells. Toxicology and applied pharmacology. Dec 15;257-(3):420-8. (2011)
DOI: 10.1016/j.taap.2011.09.026
PMid:22005276

279. Chin HW, Lindsay RC. Volatile sulfur compounds formed in disrupted tissues of different cabbage cultivars. Journal of Food Science. Jul;58(4):835-9. (1993)
DOI: 10.1111/j.1365-2621.1993.tb09370.x

280. Buttery RG, Guadagni DG, Ling LC, Seifert RM, Lipton W. Additional volatile components of cabbage, broccoli, and cauliflower. Journal of Agricultural and Food Chemistry. Jul;24(4):829-32. (1976)
DOI: 10.1021/jf60206a037

281. Whiteman M, Winyard PG. Hydrogen sulfide and inflammation: the good, the bad, the ugly and the promising. Expert review of clinical pharmacology. Jan 1;4(1):13-32. (2011)
DOI: 10.1586/ecp.10.134
PMid:22115346

282. Hine C, Harputlugil E, Zhang Y, Ruckenstuhl C, Lee BC, Brace L, Longchamp A, Treviño-Villarreal JH, Mejia P, Ozaki CK, Wang R. Endogenous hydrogen sulfide production is essential for dietary restriction benefits. Cell. Jan 15;160(1-2):132-44. (2015)
DOI: 10.1016/j.cell.2014.11.048
PMid:25542313 PMCid:PMC4297538

283. Jha S, Calvert JW, Duranski MR, Ramachandran A, Lefer DJ. Hydrogen sulfide attenuates hepatic ischemia-reperfusion injury: role of antioxidant

and antiapoptotic signaling. American Journal of Physiology-Heart and Circulatory Physiology. Aug;295(2):-H801-6. (2008)
DOI: 10.1152/ajpheart.00377.2008
PMid:18567706 PMCid:PMC2519205

284. Tripatara P, Patel NS, Collino M, Gallicchio M, Kieswich J, Castiglia S, Benetti E, Stewart KN, Brown PA, Yaqoob MM, Fantozzi R. Generation of endogenous hydrogen sulfide by cystathionine g-lyase limits renal ischemia/reperfusion injury and dysfunction. Laboratory investigation. Oct;88(10):1038-48. (2008)
DOI: 10.1038/labinvest.2008.73
PMid:18679378

285. Predmore BL, Alendy MJ, Ahmed KI, Leeuwenburgh C, Julian D. The hydrogen sulfide signaling system: changes during aging and the benefits of caloric restriction. Age. Dec 1;32(4):467-81. (2010)
DOI: 10.1007/s11357-010-9150-z
PMid:20502969 PMCid:PMC2980601

286. Pettit AP, Jonsson WO, Bargoud AR, Mirek ET, Peelor III FF, Wang Y, Gettys TW, Kimball SR, Miller BF, Hamilton KL, Wek RC. Dietary methionine restriction regulates liver protein synthesis and gene expression independently of eukaryotic initiation factor 2 phosphorylation in mice. The Journal of nutrition. Jun 1;147(6):1031-40. (2017)
DOI: 10.3945/jn.116.246710
PMid:28446632 PMCid:PMC5443467

287. Mitchell SJ, Madrigal-Matute J, Scheibye-Knudsen M, Fang E, Aon M, González-Reyes JA, Cortassa S, Kaushik S, Gonzalez-Freire M, Patel B, Wahl D. Effects of sex, strain, and energy intake on hallmarks of aging in mice. Cell metabolism. Jun 14;23(6):1093-112. (2016)
DOI: 10.1016/j.cmet.2016.05.027
PMid:27304509 PMCid:PMC4911707

288. Sikalidis AK, Stipanuk MH. Growing rats respond to a sulfur amino acid-deficient diet by phosphorylation of the a subunit of eukaryotic initiation factor 2 heterotrimeric complex and induction of adaptive components of the integrated stress response. The Journal of nutrition. Jun 1;140(6):1080-5. (2010)
DOI: 10.3945/jn.109.120428
PMid:20357079 PMCid:PMC2869497

289. Wang WJ, Cai GY, Ning YC, Cui J, Hong Q, Bai XY, Xu XM, Bu R, Sun XF, Chen XM. Hydrogen sulfide mediates the protection of dietary restriction against renal senescence in aged F344 rats. Scientific reports. Jul 26;6:30292. (2016)
DOI: 10.1038/srep30292
PMid:27456368 PMCid:PMC4960595

290. Zhang Y, Tang ZH, Ren Z, Qu SL, Liu MH, Liu LS, Jiang ZS. Hydrogen sulfide, the next potent preventive and therapeutic agent in aging and age-associated diseases. Molecular and cellular biology. Mar 15;33(6):1104-13. (2013)
DOI: 10.1128/MCB.01215-12
PMid:23297346 PMCid:PMC3592015

291. Yamamoto M, Clark JD, Pastor JV, Gurnani P, Nandi A, Kurosu H, Miyoshi M, Ogawa Y, Castrillon DH, Rosenblatt KP, Kuro-o M. Regulation of oxidative stress by the anti-aging hormone klotho. Journal of Biological Chemistry. Nov 11;280(45):38029-34. (2005)
DOI: 10.1074/jbc.M509039200
PMid:16186101 PMCid:PMC2515369

292. Chen J, Zhang H, Hu J, Gu Y, Shen Z, Xu L, Jia X, Zhang X, Ding X. Hydrogen-rich saline alleviates kidney fibrosis following AKI and retains Klotho expression. Frontiers in pharmacology. Aug 11;8:499. (2017)
DOI: 10.3389/fphar.2017.00499
PMid:28848432 PMCid:PMC5554490

293. Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, De Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. The Journals of Gerontology: Series A. Feb 1;66(2):191-201. (2011)
DOI: 10.1093/gerona/glq178
PMid:20974732 PMCid:PMC3021372

294. Yilmaz ÖH, Katajisto P, Lamming DW, Gültekin Y, Bauer-Rowe KE, Sengupta S, Birsoy K, Dursun A, Yilmaz VO, Selig M, Nielsen GP. mTORC1 in the Paneth cell niche couples intestinal stem-cell function to calorie intake. Nature. Jun;486(7404):490-5. (2012)
DOI: 10.1038/nature11163
PMid:22722868 PMCid:PMC3387287

295. Castilho RM, Squarize CH, Chodosh LA, Williams BO, Gutkind JS. mTOR mediates Wnt-induced epidermal stem cell exhaustion and aging. Cell stem cell. Sep 4;5(3):279-89. (2009)
DOI: 10.1016/j.stem.2009.06.017
PMid:19733540 PMCid:PMC2939833

296. Akunuru S, Geiger H. Aging, clonality, and rejuvenation of hematopoietic stem cells. Trends in molecular medicine. Aug 1;22(8):701-12. (2016)
DOI: 10.1016/j.molmed.2016.06.003
PMid:27380967 PMCid:PMC4969095

297. Dou X, Sun Y, Li J, Zhang J, Hao D, Liu W, Wu R, Kong F, Peng X, Li J. Short-term rapamycin treatment increases ovarian lifespan in young and middle-aged female mice. Aging Cell. Aug;16(4):825-36. (2017)
DOI: 10.1111/acel.12617
PMid:28544226 PMCid:PMC5506398

298. Bitto A, Ito TK, Pineda VV, LeTexier NJ, Huang HZ, Sutlief E, Tung H, Vizzini N, Chen B, Smith K, Meza D. Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. elife. Aug 23;5:e16351. (2016)
DOI: 10.7554/eLife.16351
PMid:27549339 PMCid:PMC4996648

299. Gong H, Qian H, Ertl R, Astle CM, Wang GG, Harrison DE, Xu X. Histone modifications change with age, dietary restriction and rapamycin treatment in mouse brain. Oncotarget. Jun 30;6(18):15882. (2015)
DOI: 10.18632/oncotarget.4137
PMid:26021816 PMCid:PMC4599244

300. Ovadya Y, Landsberger T, Leins H, Vadai E, Gal H, Biran A, Yosef R, Sagiv A, Agrawal A, Shapira A, Windheim J. Impaired immune surveillance accelerates accumulation of senescent cells and aging. Nature communications. Dec 21;9(1):1-5. (2018)
DOI: 10.1038/s41467-018-07825-3
PMid:30575733 PMCid:PMC6303397

301. da Silva PF, Ogrodnik M, Kucheryavenko O, Glibert J, Miwa S, Cameron K, Ishaq A, Saretzki G, Nagaraja-Grellscheid S, Nelson G, von Zglinicki T. The bystander effect contributes to the accumulation of senescent cells *in vivo*. Aging Cell. Feb;18(1):e12848. (2019)
DOI: 10.1111/acel.12848
PMid:30462359 PMCid:PMC6351849

302. Ogrodnik M, Kucheryavenko O, Glibert J, Miwa S, Cameron K, Ishaq A, Saretzki G, Nagaraja-Grellscheid S, Nelson G. The bystander effect contributes to the accumulation of senescent cells *in vivo*. Aging Cell. 18:e12848 (2019)
DOI: 10.1111/acel.12848
PMid:30462359 PMCid:PMC6351849

303. Korolchuk VI, Miwa S, Carroll B, Von Zglinicki T. Mitochondria in cell senescence: is mitophagy the weakest link? EBioMedicine. Jul 1;21:7-13. (2017)
DOI: 10.1016/j.ebiom.2017.03.020
PMid:28330601 PMCid:PMC5514379

304. Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, Inman CL, Ogrodnik MB, Hachfeld CM, Fraser DG, Onken JL. Senolytics improve physical function and increase lifespan in old age. Nature medicine. Aug;24(8):1246-56. (2018)
DOI: 10.1038/s41591-018-0092-9
PMid:29988130 PMCid:PMC6082705

305. Pendergrass WR, Lane MA, Bodkin NL, Hansen BC, Ingram DK, Roth GS, Yi L, Bin H, Wolf NS. Cellular proliferation potential during aging and caloric restriction in rhesus monkeys (Macaca mulatta). Journal of cellular physiology. Jul;180(1):123-30. (1999)
DOI: 10.1002/(SICI)1097-4652(199907)180:1<123::AID-JCP14>3.0.CO;2-W

306. Molofsky AV, Slutsky SG, Joseph NM, He S, Pardal R, Krishnamurthy J, Sharpless NE, Morrison SJ. Increasing p16 INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature. Sep;443(7110):448-52. (2006)
DOI: 10.1038/nature05091
PMid:16957738 PMCid:PMC2586960

307. Ressler S, Bartkova J, Niederegger H, Bartek J, Scharffetter-Kochanek K, Jansen-Dürr P, Wlaschek M. p16INK4A is a robust *in vivo* biomarker of cellular aging in human skin. Aging cell. Oct;5(5):379-89. (2006)
DOI: 10.1111/j.1474-9726.2006.00231.x
PMid:16911562

308. Herbig U, Ferreira M, Condel L, Carey D, Sedivy JM. Cellular senescence in aging primates. Science. Mar 3;311-(5765):1257. (2006)
DOI: 10.1126/science.1122446
PMid:16456035

309. Weindruch R. The retardation of aging by caloric restriction: studies in rodents and primates. Toxicologic pathology. Nov;24(6):742-5. (1996)
DOI: 10.1177/019262339602400618
PMid:8994305

310. Ogrodnik M, Miwa S, Tchkonia T, Tiniakos D, Wilson CL, Lahat A, Day CP, Burt A, Palmer A, Anstee QM, Grellscheid SN. Cellular senescence drives age-dependent hepatic steatosis. Nature communications. Jun 13;8(1):1-2. (2017)
DOI: 10.1038/ncomms15691
PMid:28608850 PMCid:PMC5474745

311. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, Van De Sluis B, Kirkland JL, van Deursen JM. Clearance of p16 Ink4a-positive senescent cells delays ageing-associated disorders. Nature. Nov;479(7372):232-6. (2011)
DOI: 10.1038/nature10600
PMid:22048312 PMCid:PMC3468323

312. Baker DJ, Childs BG, Durik M, Wijers

ME, Sieben CJ, Zhong J, Saltness RA, Jeganathan KB, Verzosa GC, Pezeshki A, Khazaie K. Naturally occurring p16 Ink4a-positive cells shorten healthy lifespan. Nature. Feb;530(7589):184-9. (2016)
DOI: 10.1038/nature16932
PMid:26840489 PMCid:PMC4845101

313. Baar MP, Brandt RM, Putavet DA, Klein JD, Derks KW, Bourgeois BR, Stryeck S, Rijksen Y, van Willigenburg H, Feijtel DA, van der Pluijm I. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell. Mar 23;169(1):132-47. (2017)
DOI: 10.1016/j.cell.2017.02.031
PMid:28340339 PMCid:PMC5556182

314. Jeon OH, Kim C, Laberge RM, Demaria M, Rathod S, Vasserot AP, Chung JW, Kim DH, Poon Y, David N, Baker DJ. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nature medicine. Jun;23(6):775. (2017)
DOI: 10.1038/nm.4324
PMid:28436958 PMCid:PMC5785239

315. Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, Janakiraman K, Sharpless NE, Ding S, Feng W, Luo Y. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nature medicine. Jan;22(1):78-83. (2016)
DOI: 10.1038/nm.4010
PMid:26657143 PMCid:PMC4762215

316. Kim EC, Kim JR. Senotherapeutics: emerging strategy for healthy aging and age-related disease. BMB reports. Jan;52(1):47. (2019)
DOI: 10.5483/BMBRep.2019.52.1.293
PMid:30526770 PMCid:PMC6386227

317. Campisi J. Aging, cellular senescence, and cancer. Annual review of physiology. Feb 10;75:685-705. (2013)
DOI: 10.1146/annurev-physiol-030212-183653
PMid:23140366 PMCid:PMC4166529

318. Van Deursen JM. The role of senescent cells in ageing. Nature. May;509(7501):439-46. (2014)
DOI: 10.1038/nature13193
PMid:24848057 PMCid:PMC4214092

319. Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. Nature reviews Molecular cell biology. Jul;15(7):482-96. (2014)
DOI: 10.1038/nrm3823
PMid:24954210

320. Zhu YI, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, O'Hara SP. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging cell. Aug;14(4):644-58. (2015)
DOI: 10.1111/acel.12344
PMid:25754370 PMCid:PMC4531078

321. Roos CM, Zhang B, Palmer AK, Ogrodnik MB, Pirtskhalava T, Thalji NM, Hagler M, Jurk D, Smith LA, Casaclang-Verzosa G, Zhu Y. Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. Aging cell. Oct;15(5):973-7. (2016)
DOI: 10.1111/acel.12458
PMid:26864908 PMCid:PMC5013022

322. Farr JN, Xu M, Weivoda MM, Monroe DG, Fraser DG, Onken JL, Negley BA, Sfeir JG, Ogrodnik MB, Hachfeld CM,

LeBrasseur NK. Targeting cellular senescence prevents age-related bone loss in mice. Nature medicine. Sep;23(9):1072-9. (2017)
DOI: 10.1038/nm.4385
PMid:28825716 PMCid:PMC5657592

323. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, Oberg AL, Birch J, Salmonowicz H, Zhu Y, Mazula DL. Cellular senescence mediates fibrotic pulmonary disease. Nature communications. Feb 23;8(1):1-1. (2017)
DOI: 10.1038/ncomms14532
PMid:28230051 PMCid:PMC5331226

324. Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ. Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature. Oct;562-(7728):578-82. (2018)
DOI: 10.1038/s41586-018-0543-y
PMid:30232451 PMCid:PMC6206507

325. Niedernhofer LJ, Robbins PD. Senotherapeutics for healthy ageing. Nature Reviews Drug Discovery. May;17(5):377. (2018)
DOI: 10.1038/nrd.2018.44
PMid:29651106

326. Yousefzadeh MJ, Zhu Y, McGowan SJ, Angelini L, Fuhrmann-Stroissnigg H, Xu M, Ling YY, Melos KI, Pirtskhalava T, Inman CL, McGuckian C. Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine. Oct 1;36:18-28. (2018)
DOI: 10.1016/j.ebiom.2018.09.015
PMid:30279143 PMCid:PMC6197652

327. Burton DG, Stolzing A. Cellular senescence: immunosurveillance and future immunotherapy. Ageing Research Reviews. May 1;43:17-25. (2018)
DOI: 10.1016/j.arr.2018.02.001
PMid:29427795

328. Sagiv A, Burton DG, Moshayev Z, Vadai E, Wensveen F, Ben-Dor S, Golani O, Polic B, Krizhanovsky V. NKG2D ligands mediate immunosurveillance of senescent cells. Aging (Albany NY). Feb;8(2):328. (2016)
DOI: 10.18632/aging.100897
PMid:26878797 PMCid:PMC4789586

329. Kang TW, Yevsa T, Woller N, Hoenicke L, Wuestefeld T, Dauch D, Hohmeyer A, Gereke M, Rudalska R, Potapova A, Iken M. Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. Nature. Nov;479(7374):547-51. (2011)
DOI: 10.1038/nature10599
PMid:22080947

330. Thapa RK, Nguyen HT, Jeong JH, Kim JR, Choi HG, Yong CS, Kim JO. Progressive slowdown/prevention of cellular senescence by CD9-targeted delivery of rapamycin using lactose-wrapped calcium carbonate nanoparticles. Scientific reports. Apr 10;7:43299. (2017)
DOI: 10.1038/srep43299
PMid:28393891 PMCid:PMC5385881

331. Nguyen HT, Thapa RK, Shin BS, Jeong JH, Kim JR, Yong CS, Kim JO. CD9 monoclonal antibody-conjugated PEGylated liposomes for targeted delivery of rapamycin in the treatment of cellular senescence. Nanotechnology. Jan 31;28(9):095101. (2017)
DOI: 10.1088/1361-6528/aa57b3
PMid:28067204

332. Kim KM, Noh JH, Bodogai M, Martindale JL, Yang X, Indig FE, Basu SK, Ohnuma K, Morimoto C, Johnson PF, Biragyn A.

Identification of senescent cell surface targetable protein DPP4. Genes & development. Aug 1;31(15):1529-34. (2017)
DOI: 10.1101/gad.302570.117
PMid:28877934 PMCid:PMC5630018

333. Roth GS, Ingram DK. Manipulation of health span and function by dietary caloric restriction mimetics. Annals of the New York Academy of Sciences. Jan;1363(1):5-10. (2016)
DOI: 10.1111/nyas.12834
PMid:26214681

334. Liu P, Zhao H, Luo Y. Anti-aging implications of Astragalus membranaceus (Huangqi): a well-known Chinese tonic. Aging and disease. Dec;8(6):868. (2017)
DOI: 10.14336/AD.2017.0816
PMid:29344421 PMCid:PMC5758356

335. Lamming DW, Ye L, Sabatini DM, Baur JA. Rapalogs and mTOR inhibitors as anti-aging therapeutics. The Journal of clinical investigation. Mar 1;123(3):980-9. (2013)
DOI: 10.1172/JCI64099
PMid:23454761 PMCid:PMC3582126

336. Si H, Liu D. Dietary antiaging phytochemicals and mechanisms associated with prolonged survival. The Journal of nutritional biochemistry. Jun 1;25(6):581-91. (2014)
DOI: 10.1016/j.jnutbio.2014.02.001
PMid:24742470 PMCid:PMC4019696

337. Chondrogianni N, Voutetakis K, Kapetanou M, Delitsikou V, Papaevgeniou N, Sakellari M, Lefaki M, Filippopoulou K, Gonos ES. Proteasome activation: an innovative promising approach for delaying aging and retarding age-related diseases. Ageing research reviews. Sep 1;23:37-55. (2015)
DOI: 10.1016/j.arr.2014.12.003
PMid:25540941

338. Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J, Wan W, Tai X. An update on inflamm-aging: mechanisms, prevention, and treatment. Journal of Immunology Research. Oct;2016. (2016)
DOI: 10.1155/2016/8426874
PMid:27493973 PMCid:PMC4963991

339. Miquel J. An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. Current pharmaceutical design. Sep 1;15(26):3003-26. (2009)
DOI: 10.2174/138161209789058110
PMid:19754376

340. Morrisette-Thomas V, Cohen AA, Fülöp T, Riesco É, Legault V, Li Q, Milot E, Dusseault-Bélanger F, Ferrucci L. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Mechanisms of ageing and development. Jul 1;139:49-57. (2014)
DOI: 10.1016/j.mad.2014.06.005
PMid:25011077 PMCid:PMC5881904

341. Desai A, Zator ZA, de Silva P, Nguyen DD, Korzenik J, Yajnik V, Ananthakrishnan AN. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. Inflammatory bowel diseases. Feb 1;19(2):309-15. (2013)
DOI: 10.1002/ibd.23026
PMid:22605668 PMCid:PMC4345352

342. Sergio G. Exploring the complex relations between inflammation and

aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty. Inflammation Research. Dec 1;57(12):558-63. (2008)
DOI: 10.1007/s00011-008-7243-2
PMid:19109735

343. Phillips AC, Carroll D, Gale CR, Lord JM, Arlt W, Batty GD. Cortisol, DHEA sulphate, their ratio, and all-cause and cause-specific mortality in the Vietnam Experience Study. European journal of endocrinology. Aug 1;163(2):285. (2010)
DOI: 10.1530/EJE-10-0299
PMid:20498139

344. Butcher SK, Killampalli V, Lascelles D, Wang K, Alpar EK, Lord JM. Raised cortisol: DHEAS ratios in the elderly after injury: potential impact upon neutrophil function and immunity. Aging cell. Dec;4(6):319-24. (2005)
DOI: 10.1111/j.1474-9726.2005.00178.x
PMid:16300484

345. Rosenfeld RS, Rosenberg BJ, Fukushima DK, Hellman L. 24-Hour secretory pattern of dehydro-isoandrosterone and dehydroisoandro-sterone sulfate. The Journal of Clinical Endocrinology & Metabolism. May 1;40(5):850-5. (1975)
DOI: 10.1210/jcem-40-5-850
PMid:123927

346. Labrie F. DHEA, important source of sex steroids in men and even more in women. InProgress in brain research Jan 1 182, 97-148. (2010)
DOI: 10.1016/S0079-6123(10)82004-7

347. Christensen H, Boysen G, Johannesen HH. Serum-cortisol reflects severity and mortality in acute stroke. Journal of the neurological sciences. Feb 15;217(2):175-80. (2004)
DOI: 10.1016/j.jns.2003.09.013
PMid:14706221

348. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. Clinical endocrinology. Jan;60(1):29-35. (2004)
DOI: 10.1111/j.1365-2265.2004.01923.x
PMid:14678284

349. Güder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, Angermann CE, Störk S. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation. Apr 3;115(13):1754-61. (2007)
DOI: 10.1161/CIRCULATIONAHA.-106.653964
PMid:17372171

350. Waters DL, Qualls CR, Dorin RI, Veldhuis JD, Baumgartner RN. Altered growth hormone, cortisol, and leptin secretion in healthy elderly persons with sarcopenia and mixed body composition phenotypes. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. May 1;63(5):536-41. (2008)
DOI: 10.1093/gerona/63.5.536
PMid:18511760

351. Trivedi DP, Khaw KT. Dehydroepiandrosterone sulfate and mortality in elderly men and women. The Journal of Clinical Endocrinology & Metabolism. Sep 1;86(9):4171-7. (2001)
DOI: 10.1210/jcem.86.9.7838
PMid:11549645

352. Mazat L, Lafont S, Berr C, Debuire B,

Tessier JF, Dartigues JF, Baulieu EE. Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. Proceedings of the National Academy of Sciences. Jul 3;98(14):8145-50. (2001)
DOI: 10.1073/pnas.121177998
PMid:11427700 PMCid:PMC35482

353. Valenti G, Denti L, Maggio M, Ceda G, Volpato S, Bandinelli S, Ceresini G, Cappola A, Guralnik JM, Ferrucci L. Effect of DHEAS on skeletal muscle over the life span: the InCHIANTI study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. May 1;59(5):M466-72. (2004)
DOI: 10.1093/gerona/59.5.M466
PMid:15123757

354. Ferrón S, Mira H, Franco S, Cano-Jaimez M, Bellmunt E, Ramírez C, Fariñas I, Blasco MA. Telomere shortening and chromosomal instability abrogates proliferation of adult but not embryonic neural stem cells. Development. Aug 15;131(16):4059-70. (2004)
DOI: 10.1242/dev.01215
PMid:15269166

355. Shay JW, Wright WE. The use of telomerized cells for tissue engineering. Nature Biotechnology. Jan;18(1):22-3. (2000)
DOI: 10.1038/71872
PMid:10625382

356. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lichtsteiner S, Wright WE. Extension of life-span by introduction of telomerase into normal human cells. science. Jan 16;279(5349):349-52. (1998)
DOI: 10.1126/science.279.5349.349
PMid:9454332

357. Robertson DM, Li L, Fisher S, Pearce VP, Shay JW, Wright WE, Cavanagh HD, Jester JV. Characterization of growth and differentiation in a telomerase-immortalized human corneal epithelial cell line. Investigative ophthalmology & visual science. Feb 1;46(2):470-8. (2005)
DOI: 10.1167/iovs.04-0528
PMid:15671271

358. Vaughan MB, Ramirez RD, Brown SA, Yang JC, Wright WE, Shay JW. A reproducible laser-wounded skin equivalent model to study the effects of aging *in vitro*. Rejuvenation Research. Jul 1;7(2):99-110. (2004)
DOI: 10.1089/1549168041552982
PMid:15312297

359. Vaughan MB, Ramirez RD, Wright WE, Minna JD, Shay JW. A three-dimensional model of differentiation of immortalized human bronchial epithelial cells. Differentiation. Apr 1;74(4):141-8. (2006)
DOI: 10.1111/j.1432-0436.2006.00069.x
PMid:16683984

360. Poh M, Boyer M, Solan A, Dahl SL, Pedrotty D, Banik SS, McKee JA, Klinger RY, Counter CM, Niklason LE. Blood vessels engineered from human cells. The Lancet. Jun 18;365(9477):2122-4. (2005)
DOI: 10.1016/S0140-6736(05)66735-9

361. Thomas M, Yang L, Hornsby PJ. Formation of functional tissue from transplanted adrenocortical cells expressing telomerase reverse

transcriptase. Nature biotechnology. Jan;18(1):39-42. (2000)
DOI: 10.1038/71894
PMid:10625388

362. Morales CP, Holt SE, Ouellette M, Kaur KJ, Yan Y, Wilson KS, White MA, Wright WE, Shay JW. Absence of cancer-associated changes in human fibroblasts immortalized with telomerase. Nature genetics. Jan;21(1):115-8. (1999)
DOI: 10.1038/5063
PMid:9916803

363. Sahin E, DePinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. nature. Mar;464(7288):520-8. (2010)
DOI: 10.1038/nature08982
PMid:20336134 PMCid:PMC3733214

364. Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, Sahin E, Kost-Alimova M, Protopopov A, Cadinanos J, Horner JW. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature. Jan;469(7328):102-6. (2011)
DOI: 10.1038/nature09603
PMid:21113150 PMCid:PMC3057569

365. Joeng KS, Song EJ, Lee KJ, Lee J. Long lifespan in worms with long telomeric DNA. Nature genetics. Jun;36(6):607-11. (2004)
DOI: 10.1038/ng1356
PMid:15122256

366. Zhu J, Wang H, Bishop JM, Blackburn EH. Telomerase extends the lifespan of virus-transformed human cells without net telomere lengthening. Proceedings of the National Academy of Sciences. Mar 30;96(7):3723-8. (1999)
DOI: 10.1073/pnas.96.7.3723
PMid:10097104 PMCid:PMC22361

367. Vera E, de Jesus BB, Foronda M, Flores JM, Blasco MA. Telomerase reverse transcriptase synergizes with calorie restriction to increase health span and extend mouse longevity. PLoS One. Jan 22;8(1):e53760. (2013)
DOI: 10.1371/journal.pone.0053760
PMid:23349740 PMCid:PMC3551964

368. Wyllie FS, Jones CJ, Skinner JW, Haughton MF, Wallis C, Wynford-Thomas D, Faragher RG, Kipling D. Telomerase prevents the accelerated cell ageing of Werner syndrome fibroblasts. Nature genetics. Jan;24(1):16-7. (2000)
DOI: 10.1038/71630
PMid:10615119

369. Shay JW, Wright WE. Hallmarks of telomeres in ageing research. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. Jan;211(2):114-23. (2007)
DOI: 10.1002/path.2090
PMid:17200948

370. Ermolaeva M, Neri F, Ori A, Rudolph KL. Cellular and epigenetic drivers of stem cell ageing. Nature Reviews Molecular Cell Biology. Sep;19(9):594. (2018)
DOI: 10.1038/s41580-018-0020-3
PMid:29858605

371. Schmidlin CJ, Dodson MB, Madhavan L, Zhang DD. Redox regulation by NRF2 in aging and disease. Free Radical Biology and Medicine. Apr 1;134:702-7. (2019)
DOI: 10.1016/j.freeradbiomed.-2019.01.016
PMid:30654017 PMCid:PMC6588470

372. Fu L, Xu X, Ren R, Wu J, Zhang W, Yang

J, Ren X, Wang S, Zhao Y, Sun L, Yu Y. Modeling xeroderma pigmentosum associated neurological pathologies with patients-derived iPSCs. Protein & cell. Mar 1;7(3):210-21. (2016)
DOI: 10.1007/s13238-016-0244-y
PMid:26874523 PMCid:PMC4791426

373. Zhang W, Li J, Suzuki K, Qu J, Wang P, Zhou J, Liu X, Ren R, Xu X, Ocampo A, Yuan T. A Werner syndrome stem cell model unveils heterochromatin alterations as a driver of human aging. Science. Jun 5;348(6239):1160-3. (2015)
DOI: 10.1126/science.aaa1356
PMid:25931448 PMCid:PMC4494668

374. Ren R, Deng L, Xue Y, Suzuki K, Zhang W, Yu Y, Wu J, Sun L, Gong X, Luan H, Yang F. Visualization of aging-associated chromatin alterations with an engineered TALE system. Cell research. Apr;27(4):483-504. (2017)
DOI: 10.1038/cr.2017.18
PMid:28139645 PMCid:PMC5385610

375. Miller JD, Ganat YM, Kishinevsky S, Bowman RL, Liu B, Tu EY, Mandal PK, Vera E, Shim JW, Kriks S, Taldone T. Human iPSC-based modeling of late-onset disease via progerin-induced aging. Cell stem cell. Dec 5;13(6):691-705. (2013)
DOI: 10.1016/j.stem.2013.11.006
PMid:24315443 PMCid:PMC4153390

376. Ding Z, Sui L, Ren R, Liu Y, Xu X, Fu L, Bai R, Yuan T, Hao Y, Zhang W, Pan H. A widely adaptable approach to generate integration-free iPSCs from non-invasively acquired human somatic cells. Protein & cell. May 1;6(5):386-9. (2015)
DOI: 10.1007/s13238-014-0117-1
PMid:25412771 PMCid:PMC4417681

377. Yang J, Li J, Suzuki K, Liu X, Wu J, Zhang W, Ren R, Zhang W, Chan P, Belmonte JC, Qu J. Genetic enhancement in cultured human adult stem cells conferred by a single nucleotide recoding. Cell research. Sep;27(9):1178-81. (2017)
DOI: 10.1038/cr.2017.86
PMid:28685772 PMCid:PMC5587854

378. Wang L, Yi F, Fu L, Yang J, Wang S, Wang Z, Suzuki K, Sun L, Xu X, Yu Y, Qiao J. CRISPR/Cas9-mediated targeted gene correction in amyotrophic lateral sclerosis patient iPSCs. Protein & cell. May 1;8(5):365-78. (2017)
DOI: 10.1007/s13238-017-0397-3
PMid:28401346 PMCid:PMC5413600

379. Huang SC, Wu TC, Yu HC, Chen MR, Liu CM, Chiang WS, Lin KM. Mechanical strain modulates age-related changes in the proliferation and differentiation of mouse adipose-derived stromal cells. BMC cell biology. Dec 1;11(1):18. (2010)
DOI: 10.1186/1471-2121-11-18
PMid:20219113 PMCid:PMC2841110

380. Pekovic V, Hutchison CJ. Adult stem cell maintenance and tissue regeneration in the ageing context: the role for A-type lamins as intrinsic modulators of ageing in adult stem cells and their niches. Journal of anatomy. Jul;213(1):5-25. (2008)
DOI: 10.1111/j.1469-7580.2008.00928.x
PMid:18638067 PMCid:PMC2475560

381. Sethe S, Scutt A, Stolzing A. Aging of mesenchymal stem cells. Ageing research reviews. Feb 1;5(1):91-116. (2006)

DOI: 10.1016/j.arr.2005.10.001
PMid:16310414

382. Stolzing A, Jones E, Mcgonagle D, Scutt A. Age-related changes in human bone marrow-derived mesenchymal stem cells: consequences for cell therapies. Mechanisms of ageing and development. Mar 1;129(3):163-73. (2008)
DOI: 10.1016/j.mad.2007.12.002
PMid:18241911

383. Zhou S, Greenberger JS, Epperly MW, Goff JP, Adler C, LeBoff MS, Glowacki J. Age-related intrinsic changes in human bone-marrow-derived mesenchymal stem cells and their differentiation to osteoblasts. Aging cell. Jun;7(3):335-43. (2008)
DOI: 10.1111/j.1474-9726.2008.00377.x
PMid:18248663 PMCid:PMC2398731

384. Gariani K, Menzies KJ, Ryu D, Wegner CJ, Wang X, Ropelle ER, Moullan N, Zhang H, Perino A, Lemos V, Kim B. Eliciting the mitochondrial unfolded protein response by nicotinamide adenine dinucleotide repletion reverses fatty liver disease in mice. Hepatology. Apr;63(4):1190-204. (2016)
DOI: 10.1002/hep.28245
PMid:26404765 PMCid:PMC4805450

385. Arantes-Oliveira N, Apfeld J, Dillin A, Kenyon C. Regulation of life-span by germ-line stem cells in Caenorhabditis elegans. Science. Jan 18;295(5554):502-5. (2002)
DOI: 10.1126/science.1065768
PMid:11799246

386. Ahmad I, Hunter RE, Flax JD, Snyder EY, Erickson RP. Neural stem cell implantation extends life in Niemann-Pick C1 mice. Journal of applied genetics. Sep 1;48(3):269-72. (2007)
DOI: 10.1007/BF03195222
PMid:17666780

387. Bernardes de Jesus B, Vera E, Schneeberger K, Tejera AM, Ayuso E, Bosch F, Blasco MA. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. EMBO molecular medicine. Aug;4(8):691-704. (2012)
DOI: 10.1002/emmm.201200245
PMid:22585399 PMCid:PMC3494070

388. Tomás-Loba A, Flores I, Fernández-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borrás C, Matheu A, Klatt P, Flores JM, Viña J. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell. Nov 14;135(4):609-22. (2008)
DOI: 10.1016/j.cell.2008.09.034
PMid:19013273

389. Cerletti M, Jang YC, Finley LW, Haigis MC, Wagers AJ. Short-term calorie restriction enhances skeletal muscle stem cell function. Cell stem cell. May 4;10(5):515-9. (2012)
DOI: 10.1016/j.stem.2012.04.002
PMid:22560075 PMCid:PMC3561899

390. Igarashi M, Guarente L. mTORC1 and SIRT1 cooperate to foster expansion of gut adult stem cells during calorie restriction. Cell. Jul 14;166(2):436-50. (2016)
DOI: 10.1016/j.cell.2016.05.044
PMid:27345368

391. Lavasani M, Robinson AR, Lu A, Song M, Feduska JM, Ahani B, Tilstra JS, Feldman CH, Robbins PD, Niedernhofer LJ, Huard J. Muscle-derived stem/progenitor cell dysfunction limits

healthspan and lifespan in a murine progeria model. Nature communications. Jan 3;3(1):1-2. (2012)
DOI: 10.1038/ncomms1611
PMid:22215083 PMCid:PMC3272577

392. Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature. Feb;433(7027):-760-4. (2005)
DOI: 10.1038/nature03260
PMid:15716955

393. Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KI, Luo J, Smith LK, Bieri G, Lin K, Berdnik D, Wabl R. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nature medicine. Jun;20(6):659-63. (2014)
DOI: 10.1038/nm.3569
PMid:24793238 PMCid:PMC4224436

394. Wahlestedt M, Norddahl GL, Sten G, Ugale A, Frisk MA, Mattsson R, Deierborg T, Sigvardsson M, Bryder D. An epigenetic component of hematopoietic stem cell aging amenable to reprogramming into a young state. Blood, The Journal of the American Society of Hematology. May 23;121(21):4257-64. (2013)
DOI: 10.1182/blood-2012-11-469080
PMid:23476050

395. Liu B, Ghosh S, Yang X, Zheng H, Liu X, Wang Z, Jin G, Zheng B, Kennedy BK, Suh Y, Kaeberlein M. Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in laminopathy-based progeria. Cell metabolism. Dec 5;16(6):738-50. (2012)
DOI: 10.1016/j.cmet.2012.11.007
PMid:23217256

396. Yang J, Li J, Suzuki K, Liu X, Wu J, Zhang W, Ren R, Zhang W, Chan P, Belmonte JC, Qu J. Genetic enhancement in cultured human adult stem cells conferred by a single nucleotide recoding. Cell research. Sep;27(9):1178-81. (2017)
DOI: 10.1038/cr.2017.86
PMid:28685772 PMCid:PMC5587854

397. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. Cell metabolism. Jun 14;23(6):1060-5. (2016)
DOI: 10.1016/j.cmet.2016.05.011
PMid:27304507 PMCid:PMC5943638

398. Li Y, Zhang W, Chang L, Han Y, Sun L, Gong X, Tang H, Liu Z, Deng H, Ye Y, Wang Y. Vitamin C alleviates aging defects in a stem cell model for Werner syndrome. Protein & cell. Jul 1;7(7):478-88. (2016)
DOI: 10.1007/s13238-016-0278-1
PMid:27271327 PMCid:PMC4930768

399. Frost B, Hemberg M, Lewis J, Feany MB. Tau promotes neurodegeneration through global chromatin relaxation. Nature neuroscience. Mar;17(3):357-66. (2014)
DOI: 10.1038/nn.3639
PMid:24464041 PMCid:PMC4012297

400. Young JI, Züchner S, Wang G. Regulation of the epigenome by vitamin C. Annual review of nutrition. Jul 17;35:545-64. (2015)
DOI: 10.1146/annurev-nutr-071714-034228
PMid:25974700 PMCid:PMC4506708

401. Oberdoerffer P, Sinclair DA. The role of nuclear architecture in genomic

instability and ageing. Nature reviews Molecular cell biology. Sep;8(9):692-702. (2007)
DOI: 10.1038/nrm2238
PMid:17700626

402. Campisi J, Vijg J. Does damage to DNA and other macromolecules play a role in aging? If so, how? Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. Feb 1;64(2):175-8. (2009)
DOI: 10.1093/gerona/gln065
PMid:19228786 PMCid:PMC2655027

403. Waddington CH. The epigenotype. International journal of epidemiology. Feb 1;41(1):10-3. (2012)
DOI: 10.1093/ije/dyr184
PMid:22186258

404. Horvath S. DNA methylation age of human tissues and cell types. Genome biology. Oct 1;14(10):3156. (2013) DOI: 10.1186/gb-2013-14-10-r115
PMid:24138928 PMCid:PMC4015143

405. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. Statistical applications in genetics and molecular biology. Aug 12;4(1). (2005)
DOI: 10.2202/1544-6115.1128
PMid:16646834

406. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nature Reviews Genetics. Jun;19(6):371. (2018)
DOI: 10.1038/s41576-018-0004-3
PMid:29643443

407. Petri MA, Mease PJ, Merrill JT, Lahita RG, Iannini MJ, Yocum DE, Ginzler EM, Katz RS, Gluck OS, Genovese MC, Van Vollenhoven R. Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus: results of a multicenter randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. Sep;50(9):2858-68. (2004)
DOI: 10.1002/art.20427
PMid:15452837

408. Phillips AC, Carroll D, Gale CR, Lord JM, Arlt W, Batty GD. Cortisol, DHEAS, their ratio and the metabolic syndrome: evidence from the Vietnam Experience Study. European journal of endocrinology. May 1;162(5):919-23. (2010)
DOI: 10.1530/EJE-09-1078
PMid:20164211

409. Chang DM, Lan JL, Lin HY, Luo SF. Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus: A multicenter randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. Nov;46(11):2924-7. (2002)
DOI: 10.1002/art.10615
PMid:12428233

410. Sawalha AH, Kovats S. Dehydroepiandrosterone in systemic lupus erythematosus. Current rheumatology reports. Aug 1;10(4):286-91. (2008)
DOI: 10.1007/s11926-008-0046-1
PMid:18662508 PMCid:PMC2701249

411. Fahy GM, Brooke RT, Watson JP, Good Z, Vasanawala SS, Maecker H, Leipold MD, Lin DT, Kobor MS, Horvath S. Reversal of epigenetic aging and immunosenescent trends in humans. Aging cell. Dec;18(6):e13028. (2019)

DOI: 10.1111/acel.13028
PMid:31496122 PMCid:PMC6826138

412. Rando OJ, Chang HY. Genome-wide views of chromatin structure. Annual review of biochemistry. Jul 7;78:245-71. (2009)
DOI: 10.1146/annurev.biochem.-78.071107.134639
PMid:19317649 PMCid:PMC2811691

413. Shen L, Wu H, Diep D, Yamaguchi S, D'Alessio AC, Fung HL, Zhang K, Zhang Y. Genome-wide analysis reveals TET- and TDG-dependent 5-methylcytosine oxidation dynamics. Cell. Apr 25;153(3):692-706. (2013)
DOI: 10.1016/j.cell.2013.04.002
PMid:23602152 PMCid:PMC3687516

414. Wu H, D'Alessio AC, Ito S, Wang Z, Cui K, Zhao K, Sun YE, Zhang Y. Genome-wide analysis of 5-hydroxy-methylcytosine distribution reveals its dual function in transcriptional regulation in mouse embryonic stem cells. Genes & development. Apr 1;25(7):679-84. (2011)
DOI: 10.1101/gad.2036011
PMid:21460036 PMCid:PMC3070931

415. Ruthenburg AJ, Allis CD, Wysocka J. Methylation of lysine 4 on histone H3: intricacy of writing and reading a single epigenetic mark. Molecular cell. Jan 12;25(1):15-30. (2007)
DOI: 10.1016/j.molcel.2006.12.014
PMid:17218268

416. Bonasio R, Tu S, Reinberg D. Molecular signals of epigenetic states. science. Oct 29;330(6004):612-6. (2010)
DOI: 10.1126/science.1191078
PMid:21030644 PMCid:PMC3772643

417. Stuwe E, Toth KF, Aravin AA. Small but sturdy: small RNAs in cellular memory and epigenetics. Genes & development. Mar 1;28(5):423-31. (2014)
DOI: 10.1101/gad.236414.113
PMid:24589774 PMCid:PMC3950340

418. Hung T, Chang HY. Long noncoding RNA in genome regulation: prospects and mechanisms. RNA biology. Sep 1;7(5):582-5. (2010)
DOI: 10.4161/rna.7.5.13216
PMid:20930520 PMCid:PMC3073254

419. Wang MC, O'Rourke EJ, Ruvkun G. Fat metabolism links germline stem cells and longevity in C. elegans. Science. Nov 7;322(5903):957-60. (2008)
DOI: 10.1126/science.1162011
PMid:18988854 PMCid:PMC2760269

420. Young RA. Control of the embryonic stem cell state. Cell. Mar 18;144(6):940-54. (2011)
DOI: 10.1016/j.cell.2011.01.032
PMid:21414485 PMCid:PMC3099475

421. Rando OJ, Verstrepen KJ. Timescales of genetic and epigenetic inheritance. Cell. Feb 23;128(4):655-68. (2007)
DOI: 10.1016/j.cell.2007.01.023
PMid:17320504

422. Dodd IB, Micheelsen MA, Sneppen K, Thon G. Theoretical analysis of epigenetic cell memory by nucleosome modification. Cell. May 18;129(4):813-22. (2007)
DOI: 10.1016/j.cell.2007.02.053
PMid:17512413

423. Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, Klotzle B, Bibikova M, Fan JB, Gao Y, Deconde R. Genome-wide methylation profiles reveal quantitative views of human aging rates. Molecular cell. Jan 24;49(2):359-67.

(2013)
DOI: 10.1016/j.molcel.2012.10.016
PMid:23177740 PMCid:PMC3780611

424. Marioni RE, Shah S, McRae AF, Chen BH, Colicino E, Harris SE, Gibson J, Henders AK, Redmond P, Cox SR, Pattie A. DNA methylation age of blood predicts all-cause mortality in later life. Genome biology. Dec;16(1):1-2. (2015)
DOI: 10.1186/s13059-015-0584-6
PMid:25633388 PMCid:PMC4350614

425. Feng S, Jacobsen SE, Reik W. Epigenetic reprogramming in plant and animal development. Science. Oct 29;330(6004):622-7. (2010)
DOI: 10.1126/science.1190614
PMid:21030646 PMCid:PMC2989926

426. Meissner A. Epigenetic modifications in pluripotent and differentiated cells. Nature biotechnology. Oct;28(10):1079-88. (2010)
DOI: 10.1038/nbt.1684
PMid:20944600

427. Vastenhouw NL, Zhang Y, Woods IG, Imam F, Regev A, Liu XS, Rinn J, Schier AF. Chromatin signature of embryonic pluripotency is established during genome activation. Nature. Apr;464(7290):922-6. (2010)
DOI: 10.1038/nature08866
PMid:20336069 PMCid:PMC2874748

428. Yan J, Chen SA, Local A, Liu T, Qiu Y, Dorighi KM, Preissl S, Rivera CM, Wang C, Ye Z, Ge K. Histone H3 lysine 4 monomethylation modulates long-range chromatin interactions at enhancers. Cell research. Feb;28(2):204-20. (2018)
DOI: 10.1038/cr.2018.1
PMid:29313530 PMCid:PMC5799818

429. Rada-Iglesias A, Bajpai R, Swigut T, Brugmann SA, Flynn RA, Wysocka J. A unique chromatin signature uncovers early developmental enhancers in humans. Nature. Feb;470(7333):279-83. (2011)
DOI: 10.1038/nature09692
PMid:21160473 PMCid:PMC4445674

430. Creyghton MP, Cheng AW, Welstead GG, Kooistra T, Carey BW, Steine EJ, Hanna J, Lodato MA, Frampton GM, Sharp PA, Boyer LA. Histone H3K27ac separates active from poised enhancers and predicts developmental state. Proceedings of the National Academy of Sciences. 107(50):21931-6. (2010)
DOI: 10.1073/pnas.1016071107
PMid:21106759 PMCid:PMC3003124

431. Miao YL, Kikuchi K, Sun QY, Schatten H. Oocyte aging: cellular and molecular changes, developmental potential and reversal possibility. Human reproduction update. 2009 Sep 1;15(5):573-85. (2010)
DOI: 10.1093/humupd/dmp014
PMid:19429634

432. Rajfer J. Sperm health in the aging male. Reviews in urology. 8(2):87. (2006)

433. Smith ZD, Chan MM, Mikkelsen TS, Gu H, Gnirke A, Regev A, Meissner A. A unique regulatory phase of DNA methylation in the early mammalian embryo. Nature. Apr;484(7394):339-44. (2012)
DOI: 10.1038/nature10960
PMid:22456710 PMCid:PMC3331945

434. Briggs R, King TJ. Transplantation of living nuclei from blastula cells into enucleated frogs' eggs. Proceedings of the National Academy of Sciences. May 1;38(5):455-63. (1952)
DOI: 10.1073/pnas.38.5.455

PMid:16589125 PMCid:PMC1063586

435. King TJ, Briggs R. Transplantation of living nuclei of late gastrulae into enucleated eggs of Rana pipiens. Development. Mar 1;2(1):73-80. (1954)

436. Gurdon JB. Adult frogs derived from the nuclei of single somatic cells. Developmental biology. Apr 1;4(2):256-73. (1962)
DOI: 10.1016/0012-1606(62)90043-X

437. Gurdon JB. Changes in somatic cell nuclei inserted into growing and maturing amphibian oocytes. Development. Nov 1;20(3):401-14. (1968)

438. Gurdon JB. Nuclear transplantation and the control of gene activity in animal development. Proceedings of the Royal Society of London. Series B. Biological Sciences. Dec 1;176(1044):303-14. (1970)
DOI: 10.1098/rspb.1970.0050
PMid:4395100

439. Campbell KH, McWhir J, Ritchie WA, Wilmut I. Sheep cloned by nuclear transfer from a cultured cell line. Nature. Mar;380(6569):64-6. (1996)
DOI: 10.1038/380064a0
PMid:8598906

440. Rideout WM, Eggan K, Jaenisch R. Nuclear cloning and epigenetic reprogramming of the genome. Science. Aug 10;293(5532):1093-8. (2001)
DOI: 10.1126/science.1063206
PMid:11498580

441. Greer EL, Maures TJ, Ucar D, Hauswirth AG, Mancini E, Lim JP, Benayoun BA, Shi Y, Brunet A. Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans. Nature. Nov;479(7373):365-71. (2011)
DOI: 10.1038/nature10572
PMid:22012258 PMCid:PMC3368121

442. Lee JH, Bugarija B, Millan EJ, Walton NM, Gaetz J, Fernandes CJ, Yu WH, Mekel-Bobrov N, Vallender TW, Snyder GE, Xiang AP. Systematic identification of cis-silenced genes by trans complementation. Human molecular genetics. Mar 1;18(5):835-46. (2009)
DOI: 10.1093/hmg/ddn409
PMid:19050040 PMCid:PMC2640206

443. Lee JH, Gaetz J, Bugarija B, Fernandes CJ, Snyder GE, Bush EC, Lahn BT. Chromatin analysis of occluded genes. Human molecular genetics. Jul 15;18(14):2567-74. (2009)
DOI: 10.1093/hmg/ddp188
PMid:19380460 PMCid:PMC2701328

444. Terranova R, Pereira CF, Du Roure C, Merkenschlager M, Fisher AG. Acquisition and extinction of gene expression programs are separable events in heterokaryon reprogramming. Journal of cell science. May 15;119(10):2065-72. (2006)
DOI: 10.1242/jcs.02945
PMid:16638804

445. Piccolo FM, Pereira CF, Cantone I, Brown K, Tsubouchi T, Soza-Ried J, Merkenschlager M, Fisher AG. Using heterokaryons to understand pluripotency and reprogramming. Philosophical Transactions of the Royal Society B: Biological Sciences. Aug 12;366(1575):2260-5. (2011)
DOI: 10.1098/rstb.2011.0004
PMid:21727131 PMCid:PMC3130413

446. Cowan CA, Atienza J, Melton DA, Eggan K. Nuclear reprogramming of somatic

cells after fusion with human embryonic stem cells. Science. 309(5739):1369-73. (2005)
DOI: 10.1126/science.1116447
PMid:16123299

447. Tada M, Takahama Y, Abe K, Nakatsuji N, Tada T. Nuclear reprogramming of somatic cells by *in vitro* hybridization with ES cells. Current Biology. Oct 2;11(19):1553-8. (2001)
DOI: 10.1016/S0960-9822(01)00459-6

448. Donohoe ME, Silva SS, Pinter SF, Xu N, Lee JT. The pluripotency factor Oct4 interacts with Ctcf and also controls X-chromosome pairing and counting. Nature. Jul;460(7251):128-32. (2009)
DOI: 10.1038/nature08098
PMid:19536159 PMCid:PMC3057664

449. Navarro P, Chambers I, Karwacki-Neisius V, Chureau C, Morey C, Rougeulle C, Avner P. Molecular coupling of Xist regulation and pluripotency. Science. Sep 19;321(5896):1693-5. (2008)
DOI: 10.1126/science.1160952
PMid:18802003

450. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. cell. Aug 25;126(4):663-76. (2006)
DOI: 10.1016/j.cell.2006.07.024
PMid:16904174

451. Krishnamurthy J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su L, Sharpless NE. Ink4a/Arf expression is a biomarker of aging. The Journal of clinical investigation. Nov 1;114(9):1299-307. (2004)
DOI: 10.1172/JCI22475
PMid:15520862 PMCid:PMC524230

452. Stadtfeld M, Hochedlinger K. Induced pluripotency: history, mechanisms, and applications. Genes & development. Oct 15;24(20):2239-63. (2010)
DOI: 10.1101/gad.1963910
PMid:20952534 PMCid:PMC2956203

453. Loh KM, Lim B. Recreating pluripotency? Cell Stem Cell. Aug 6;7(2):137-9. (2010)
DOI: 10.1016/j.stem.2010.07.005
PMid:20682438

454. Ouyang Z, Zheng GX, Chang HY. Noncoding RNA landmarks of pluripotency and reprogramming. Cell stem cell. Dec 3;7(6):649-50. (2010)
DOI: 10.1016/j.stem.2010.11.018
PMid:21112559 PMCid:PMC3027494

455. Mikkelsen TS, Hanna J, Zhang X, Ku M, Wernig M, Schorderet P, Bernstein BE, Jaenisch R, Lander ES, Meissner A. Dissecting direct reprogramming through integrative genomic analysis. Nature. Jul;454(7200):49-55. (2008)
DOI: 10.1038/nature07056
PMid:18509334 PMCid:PMC2754827

456. Wahlestedt M, Norddahl GL, Sten G, Ugale A, Frisk MA, Mattsson R, Deierborg T, Sigvardsson M, Bryder D. An epigenetic component of hematopoietic stem cell aging amenable to reprogramming into a young state. Blood, The Journal of the American Society of Hematology. May 23;121(21):4257-64. (2013)
DOI: 10.1182/blood-2012-11-469080
PMid:23476050

457. Mertens J, Paquola AC, Ku M, Hatch E, Böhnke L, Ladjevardi S, McGrath S, Campbell B, Lee H, Herdy JR, Gonçalves JT. Directly reprogrammed human neurons retain aging-associated

transcriptomic signatures and reveal age-related nucleocytoplasmic defects. Cell stem cell. Dec 3;17(6):705-18. (2015)
DOI: 10.1016/j.stem.2015.09.001
PMid:26456686 PMCid:PMC5929130

458. Yoshida GJ. Emerging roles of Myc in stem cell biology and novel tumor therapies. Journal of Experimental & Clinical Cancer Research. Dec;37(1):173. (2018)
DOI: 10.1186/s13046-018-0964-3
PMid:30477547 PMCid:PMC6258388

459. Wei Z, Yang Y, Zhang P, Andrianakos R, Hasegawa K, Lyu J, Chen X, Bai G, Liu C, Pera M, Lu W. Klf4 interacts directly with Oct4 and Sox2 to promote reprogramming. Stem cells. Dec;27(12):2969-78. (2009)
DOI: 10.1002/stem.231
PMid:19816951

460. Lapasset L, Milhavet O, Prieur A, Besnard E, Babled A, Aït-Hamou N, Leschik J, Pellestor F, Ramirez JM, De Vos J, Lehmann S. Rejuvenating senescent and centenarian human cells by reprogramming through the pluripotent state. Genes & development. Nov 1;25(21):2248-53. (2011)
DOI: 10.1101/gad.173922.111
PMid:22056670 PMCid:PMC3219229

461. Christen B, Robles V, Raya M, Paramonov I, Belmonte JC. Regeneration and reprogramming compared. BMC biology. Dec 1;8(1):5. (2010)
DOI: 10.1186/1741-7007-8-5
PMid:20089153 PMCid:PMC2826312

462. Tiscornia G, Belmonte JC. MicroRNAs in embryonic stem cell function and fate. Genes & development. Dec 15;24(24):2732-41. (2010)
DOI: 10.1101/gad.1982910
PMid:21159814 PMCid:PMC3003189

463. Liu GH, Suzuki K, Qu J, Sancho-Martinez I, Yi F, Li M, Kumar S, Nivet E, Kim J, Soligalla RD, Dubova I. Targeted gene correction of laminopathy-associated LMNA mutations in patient-specific iPSCs. Cell stem cell. Jun 3;8(6):688-94. (2011)
DOI: 10.1016/j.stem.2011.04.019
PMid:21596650 PMCid:PMC3480729

464. Kubben N, Misteli T. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. Nature Reviews Molecular Cell Biology. Oct;18(10):595. (2017)
DOI: 10.1038/nrm.2017.68
PMid:28792007 PMCid:PMC6290461

465. Yang J, Cai N, Yi F, Liu GH, Qu J, Belmonte JC. Gating pluripotency via nuclear pores. Trends in molecular medicine. Jan 1;20(1):1-7. (2014)
DOI: 10.1016/j.molmed.2013.10.003
PMid:24211182

466. Krizhanovsky V, Lowe SW. The promises and perils of p53. Nature. Aug;460(7259):1085-6. (2009)
DOI: 10.1038/4601085a
PMid:19713919 PMCid:PMC2974062

467. Agarwal S, Loh YH, McLoughlin EM, Huang J, Park IH, Miller JD, Huo H, Okuka M, Dos Reis RM, Loewer S, Ng HH. Telomere elongation in induced pluripotent stem cells from dyskeratosis congenita patients. Nature. Mar;464(7286):292-6. (2010)
DOI: 10.1038/nature08792
PMid:20164838 PMCid:PMC3058620

468. Batista LF, Pech MF, Zhong FL, Nguyen HN, Xie KT, Zaug AJ, Crary SM, Choi J,

Sebastiano V, Cherry A, Giri N. Telomere shortening and loss of self-renewal in dyskeratosis congenita induced pluripotent stem cells. Nature. Jun;474(7351):399-402. (2011)
DOI: 10.1038/nature10084
PMid:21602826 PMCid:PMC3155806

469. Mahmoudi S, Brunet A. Aging and reprogramming: a two-way street. Current opinion in cell biology. Dec 1;24(6):744-56. (2012)
DOI: 10.1016/j.ceb.2012.10.004
PMid:23146768 PMCid:PMC3540161

470. Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. Cell. Jan 20;148(1-2):46-57. (2012)
DOI: 10.1016/j.cell.2012.01.003
PMid:22265401 PMCid:PMC3336960

471. Kurian L, Sancho-Martinez I, Nivet E, Aguirre A, Moon K, Pendaries C, Volle-Challier C, Bono F, Herbert JM, Pulecio J, Xia Y. Conversion of human fibroblasts to angioblast-like progenitor cells. Nature methods. Jan;10(1):77. (2013)
DOI: 10.1038/nmeth.2255
PMid:23202434 PMCid:PMC3531579

472. Thier M, Wörsdörfer P, Lakes YB, Gorris R, Herms S, Opitz T, Seiferling D, Quandel T, Hoffmann P, Nöthen MM, Brüstle O. Direct conversion of fibroblasts into stably expandable neural stem cells. Cell stem cell. Apr 6;10(4):473-9. (2012)
DOI: 10.1016/j.stem.2012.03.003
PMid:22445518

473. Ocampo A, Reddy P, Belmonte JC. Anti-aging strategies based on cellular reprogramming. Trends in molecular medicine. Aug 1;22(8):725-38. (2016)
DOI: 10.1016/j.molmed.2016.06.005
PMid:27426043

474. Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, Li M, Lam D, Kurita M, Beyret E, Araoka T. *In vivo* amelioration of age-associated hallmarks by partial reprogramming. Cell. Dec 15;167(7):-1719-33. (2016)
DOI: 10.1016/j.cell.2016.11.052
PMid:27984723 PMCid:PMC5679279

475. Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, Li M, Lam D, Kurita M, Beyret E, Araoka T. *In vivo* amelioration of age-associated hallmarks by partial reprogramming. Cell. Dec 15;167(7):1719-33. (2016)
DOI: 10.1016/j.cell.2016.11.052
PMid:27984723 PMCid:PMC5679279

476. Osorio FG, Navarro CL, Cadiñanos J, López-Mejía IC, Quirós PM, Bartoli C, Rivera J, Tazi J, Guzmán G, Varela I, Depetris D. Splicing-directed therapy in a new mouse model of human accelerated aging. Science translational medicine. Oct 26;3(106):106ra107. (2011)
DOI: 10.1126/scitranslmed.3002847
PMid:22030750

477. Scaffidi P, Misteli T. Reversal of the cellular phenotype in the premature aging disease Hutchinson-Gilford progeria syndrome. Nature medicine. Apr;11(4):440-5. (2005)
DOI: 10.1038/nm1204
PMid:15750600 PMCid:PMC1351119

478. Sarkar TJ, Quarta M, Mukherjee S, Colville A, Paine P, Doan L, Tran CM, Chu CR, Horvath S, Qi LS, Bhutani N.

Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells. Nature communications. Mar 24;11(1):1-2. (2020)
DOI: 10.1038/s41467-020-15174-3
PMid:32210226 PMCid:PMC7093390

Abbreviations: Dietary restriction (DR), Calorie restriction (CR), AMP-activated protein kinase (AMPK), *Caenorhabditis elegans* (*C. elegans*), Essential amino acids (EAA), Cerbrovascular accident (CVD), 8-oxo-2-deoxyguanosine (oxo^8dG), Nuclear DNA (nDNA), Mitochondrial DNA (mtDNA), Oxidative phosphorylation (OXPHOS), Nicotinamide adenine dinucleotide (NAD), tryptophan (Trp), Nicotinamide (NAM), Nicotinamide mononucleotide (NMN), Nicotinamide riboside (NR), 5′-phosphoribosyl-1-pyrophosphate (PRPP), NR kinases (NRKs), NMN adenylyl transferases (NMNATs), NMN adenylyltransferases (NMNAT1-3), Nicotinamide phosphoribosyltransferase (Nampt), β-amyloid (Aβ), S-adenosyl methionine (SAM), Carnosine (beta-alanyl-L-histidine), IκB kinase complex (IKK), N-*tert*-butyl-*α*-phenylnitrone (PBN), Hydrogen sulfide (H_2S), Transsulfuration pathway (TSP), Manganese superoxide dismutase (SOD), Age-Related Diseases (ARDs), Histone deacetylase (HDAC), Dipeptidyl peptidase 4 (DPP4), Human umbilical cord endothelial cells (HUVEC), Janus kinase (JAK), Interluekin (IL), Tumor necrsis factor (TNF), Dehydroepiandrosterone (DHEA), 4-hydroxytamoxifen (4-OHT), Insulin growth factor (IGF), Muscle-derived stem/progenitor cells (MDSPCs), Nuclear factor erythroid 2-related factor (NRF2), Somatic cell nuclear transfer (SCNT), Human embryonic stem cells (hES), Muscle stem cells (MuSCs), OCT4, SOX2, KLF4, c-MYC, (OSKM), OCT4, SOX2, KLF4, c-MYC, LIN28, NANOG (OSKMLN), Embryonic stem cells (ESC), Induced pluripotent cells (iPS), Growth and differentiation factor (GDF), Senescence-associated mitochondrial dysfunction (SAMD), Senescence-Associated Secretory Phenotype (SASP), Reactive oxygen species (ROS), Hutchinson-Gilford progeria syndrome (HGPS), Werner Syndrome (WS), Duchenne Muscular Dystrophy (DMD) , Unfolded protein response (UPR^{mt}), poly-ADP-ribosylation (PARylation), Poly(ADP-ribose) polymerase protein (PARP), Clustered regularly interspaced short palindromic repeats (CRISPR)

Key Words: Aging, Senescence, Immuno-senescence, Treatment, Senotherapeutics, Senolytics, Senomorphics, Anti-Inflammaging, Aging Reversal, Review

Send correspondence to: Siamak Tabib-zadeh, Frontiers in Bioscience Research Institute in Aging and Cancer, 16471 Scientific Way, Irvine, CA 92618, Tel: 949-715-8286, E-mail: fbs@bioscience.org