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ANTI-AGING GENE THERAPY STUDIES ON MODEL ORGANISMS

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ABSTRACT

Experiments conducted in different model systems show that gene therapy can extend the life span of an organism. Various genetic interventions, which include mutation, knockout, and overexpression, led to the extension of life span in *Caenorhabditis*, *Drosophila melanogaster*, mouse, yeast, and even human cell lines. Our literature review revealed that few aging theories could be used as an excellent tool to increase longevity, and delay aging in an organism. In this review, we have provided a brief view of the majority of genetic therapies done on model organisms from 1980 to 2018 as an anti-aging treatment.

Key-words: Aging, Gene therapy, Gerontogenes, Longevity, Model Organisms

INTRODUCTION

Gene therapy refers to the process in which a therapeutic gene segment is added to replace the existing mutated gene segment in the genome for curing genetic deficiency (Dunbar *et al*., 2018). During the early 1960s and 1970s, initial concepts of gene therapy were originated. During this time, the production of genetically marked cell lines and work on mechanisms of transformation of the cell with the help of Simian virus 40 (SV40) and Papova viruses polyoma was in progress. The availability of cloned genes was easy due to the introduction of recombinant DNA techniques, and it helped in explaining how phenotypic diseases and defects can be cured using foreign genes in in-vitro conditions, especially in mammalian cells. This was further demonstrated by using retroviral vectors, and so gene therapy became a widely recognized technique in human patients (Hanna *et al*., 2017; Lundstrom, 2018). Since the 1980s, the field of molecular biology is developed rapidly. Human genome sequencing and gene cloning have already been achieved. Gene therapy is becoming an acceptable method to produce proteins that a person cannot produce in a specific condition, for instance, insulin for diabetic patients.

Moreover, scientists also introduced genes directly into humans to cure diseases caused by a defect in single genes such as Chronic granulomatous disease (Keller *et al*., 2018), muscular dystrophy (Chamberlain *et al*., 2017), Gaucher Disease (Mistry *et al*., 2017), hemophilia (Kohn, 2019), Hypercholesterolemia (Rotondo *et al*., 2017), Alpha-1 antitrypsin (Mueller *et al*., 2017), cystic fibrosis (Hart *et al*., 2017) and sickle cell anemia (Kohn, 2019). The term 'gene therapy' could be referred to as the transmittance of the therapeutic exogenous nucleic acids in order to either ameliorate a disease or for its complete remedy. All these activities point towards its therapeutic function in order to amend the patient's metabolic and physiological functioning. However, apart from their gene therapeutic properties, this technique is significantly exploited to invigorate various geriatric conditions by rejuvenating telomerase sequences, activating or inhibiting those sectors of genes that either impede or aggravate age associated illnesses causing a substantial decline in aging and disease progression. However, few studies have been conducted in humans since bioethical specialists highly content these techniques because of its use for beautification and biohacking purposes, making an individual vulnerable to potentially toxic and adverse effects and also its molecular mechanism in impeding the onset of aging is still elusive to the scientific community. Therefore, attempts have been made to elucidate the effect of gene therapy in hijacking the aging process and also to unravel those proteins and gene regions that modulate the aging process by adopting various model organisms. In this review, we gathered literature regarding the role of gene therapy in prolonging life expectancy and preventing age-associated illnesses.

AGING

In biology, aging can be defined as progressive senescence of cells, tissues, and molecules which affect physiological and functional attributes essential for persistence and reproduction. It is a complex process that is determined by environmental and genetic factors (Janac *et al*., 2017). This leads to a decline in the capacity of an organism to maintain and control homeostasis under stress conditions. Aging inevitably leads to death, and its duration varies from individual to individual but eventually increases the vulnerability to several age-related anomalies. All major diseases in humans, such as dementia, osteoporosis, cataract, cancer, muscular degeneration,

atherosclerosis, diabetes-II, and excessive muscle loss leading to sarcopenia, have aging as their cause (Wei *et al*., 2017). "Biogerontology" has revealed that with aging, changes occur in macromolecules, organisms, cells, organs, and tissues (Larsen, 2019). However, other studies also show that changes can be made in the rate of aging and life length. As for biological processes, the fundamental and elemental units of information are "genes." Thus, the ideal anti-aging treatment can be the "gene therapy".

THEORIES OF AGING

Few theories of aging have been given that explain the process of aging and its possible cause.

DNA DAMAGE THEORY

Several repeats of nucleotides in a specific manner make up genes, and these genes encode for proteins, RNAs, and other polymeric materials critical for survival and reproductive health. From a molecular perspective, the sequences present within these genes are susceptible to various intricate mutations levied by internal and environmental agents. To repair the error ensued by these agencies, organisms have devised a DNA inspection system to deal with any spontaneous or deleterious mutation that might lead to any adverse consequence.

According to DNA damage theory, DNA sequences are vulnerable to mutation, which can result in the development of mutated protein, RNA, or enzyme. As a consequence, these mutated entities disrupt the structural and functional integrity of various complicated cellular pathways, hence capitulate to aging. This theory is supported by different findings such as irradiating somatic cells reduces their survival expectancy (Amaro-Ortiz *et al*., 2014; Panich *et al*., 2016; Radman, 2016), progressive cells ageing plummet their normal function due to their amiable nature to mutate (Bhatia-Dey *et al*., 2016). A gradual increase in age increases the risk for somatic and chromosomal mutation, responsible for pre-aging syndromes (Gorbunova *et al*., 2016; Pan *et al*., 2016; Wiley *et al*., 2016). Different research findings provided supportive justification that DNA Damage causes aging and other functions to decline, but further studies are underway to establish a strong link between DNA damage and aging (Gassen *et al*., 2017; Sidler *et al*., 2017).

MITOCHONDRIAL DNA DAMAGE THEORY

This theory states that; inevitable cell maturation provokes the production and accumulation of reactive oxygen species, which adversely interact with mitochondrial DNA inducing irreparable DNA adulteration and affliction to mitochondrial energy-generating functions.

The genomic infrastructure of mitochondria comprised of double-stranded, supercoiled circular DNA encapsulated with mitochondrial proteins known as nucleoids. This protective encapsulation as compared to nuclear DNA, a fragile barrier that makes them defenseless against mutagens and the repair system of mitochondria, is ten times more likely to inculcate deleterious mutation in mitochondrial DNA (mtDNA) (Pinto *et al*., 2015). Also, the location and distribution of mitochondrial nucleoids lie close to the mitochondrial respiratory chain, which is a principal source of reactive oxygen species, increases the chances of mtDNA damage up to ten folds (Giorgi *et al*., 2018; Nissanka *et al*., 2018).

These anomalies fail to fulfill the actual energy requirement, and increased accumulation of ROS and other genotoxic materials contribute to the gradual aging onset and trigger cellular apoptosis. This theory is considerably weighed by those aging disorders in which mitochondrial dysfunction and mtDNA mutations was the main culprit (Kauppila *et al*., 2017; Srivastava, 2017; Theurey *et al*., 2018).

THE TELOMERE THEORY

Telomere shortening is the principal of aging that impedes DNA replication which in turn inflict cell replacement and organ/tissue renewal. With continuous DNA replication, DNA polymerase unable to extend a segment of DNA, thus leaving underdeveloped DNA, vulnerable to nucleases activity. To protect DNA from these nucleases, Telomere, a repetitive tandem repeat found at the ends of each chromosome, provides complementary nucleotides sequences to recuperate with the loss generated by DNA polymerase. However, these telomeric sequences are not unlimited as with every replication; these sequences are prone to shortening, results in replication senescence.

On the other hand, stem cells and gonadal cells are actively dividing cells and possess a specialized enzyme in high concentration known as Telomerase, preserve the DNA integrity of these cells from nucleases by maintaining constant telomeric length and prolong replicative lifespan. However, this enzyme is present at low concentrations in somatic cells.

There is corroborating evidence confirm that cell age can be determined by the length of the Telomere (Blackburn *et al*., 2015; Simons, 2015) which is reflected in those individuals suffering from Hutchinson Gilford

Progeria syndrome, a debilitating genetic disorder in which an individual age faster due to minuscule length of Telomeres (Ahmed *et al*., 2018). However, this theory reacts differently in case of cancer and other immortal cells in which telomerase enzymes consistently revive adequate telomeric length to resist cellular and replicative senescence (Piano *et al*., 2015; Aunan *et al*., 2017). Conversely, cellular senescence is inflicted by dysregulated gene expression that happens with an age-related chronic disease that provokes a pro-inflammatory state leading to death (Lasry *et al*., 2015). However, the available literature does not fully satisfy the scientific community that length of the telomere is linked to life span, as the telomeric length of mouse chromosomes are more lengthy as compared to humans (Muñoz-Lorente *et al*., 2019) and also replicative senescence is controlled by telomerase enzyme. In contrast, there are other pathways involved in inducing cellular senescence (Liu *et al*., 2019).

ERROR CATASTROPHE THEORY

This theory posits that Random errors in biosynthetic systems responsible for the transfer of DNA encoded messages (proteins, RNAs) give rise to abnormal, mutated entities that jeopardize and extenuate synthesis fidelity with increasing age and accelerate the process of aging.

According to this theory, there is an equilibrium exists in between intricate biosynthetic processes in which spontaneous errors happen in transcription, proofreading, translation, splicing, RNA transport, folding and conformation setting of polypeptides and proteins and it happens to be related with age (Milholland *et al*., 2017; Fedarko, 2018). However, these mutations attain considerable speed when these biosynthetic machinery gets destabilized with increasing age, which causes error rate to proliferate, hence compromises the cell's macromolecular function and exacerbate aging. However, this theory is in the initial stages of testing, and it has been applied to various pathological conditions to authenticate its validity and correlation with aging.

TRANSPOSONS ACTIVATION THEORY

According to Transposons Activation Theory, progressive increase in ageing upregulates the activity of transposable elements which in turn elevate the chances of somatic mutation causing aging symptoms (Loreto *et al*., 2017; Erwin *et al*., 2019)

Transposons are genetic elements present in the genome of an organism that allows specific DNA sequences to shift themselves from one part of the genome to another, and their subsequent incorporation in different DNA sequence causes mutagenesis. The reason behind this random insertion is to ameliorate an individual both physical and evolutionary point but, at the same time, inflict genomic instability, replication errors, and DNA damage (Sturm *et al*., 2015; Helfand *et al*., 2017). This problem is efficiently dealt with by various intricate repair mechanisms that suppress such sequences to shift. However, these repair mechanisms seem to fade with increasing age, energizes the transposons activity, and its subsequent activation leads to incite cell senescence and progressive dysfunction of aging cells (Wood *et al*., 2013; Orr, 2016). Such observation was seen in *Drosophila* by increasing the activation of transposons caused gradual degeneration of memory functions and decreased its life expectancy (Li *et al*., 2013).

MUTATION AND OVEREXPRESSION OF GENES ASSOCIATION WITH LONGEVITY
MUTATION

In *Caenorhabditis elegans* (nematode), the first gene mutation, which resulted in the extension of the lifespan, was identified. After that large number of the genes were experimentally mutated, which on the loss of their respective functions resulted in the extension of the lifespan of the organism. These longevity genes have been reported in *Drosophila melanogaster*, *C. elegans*, rodents, and yeast (Proshkina *et al*., 2015; Yanai *et al*., 2017). Induction of mutations and deletions by chemical mutagens and irradiation, reduction in gene expression by RNAi induces abrogation of translation and gene expression alteration by knockout and by homologous recombination are the methods which were used for the identification of such longevity genes (Panowski *et al*., 2007; Rattan, 2007; Rattan *et al*., 2008, 2009). It is important to note that when the activity of one or more genes was reduced or stopped by intervention, the result was increased life span (Rattan, 2007; Rattan *et al*., 2008, 2009).

OVEREXPRESSION OF GENES

The extension of life span in different model systems rodents, *Drosophila melanogaster*, cultured cells, and worms occurred due to increased expression of gene products, which is done by transgenic manipulation, i.e., the addition of one or multiple copies of various genes (Yanai *et al*., 2017). Several genes, such as antioxidant genes and stress response genes whose overexpression in some model systems results in the extension of life span (Blackwell *et al*., 2015; Zhang *et al*., 2015; Loboda *et al*., 2016). The ectopic expression of telomerase in a wide variety of cells is one of the most widely used genetic intervention for extension of the lifespan of healthy cells, however, in vivo

injection of such genetically modified cells often leads to transformation, instability, and cancer forming activities (Larrick *et al*., 2015; Jäger *et al*., 2016; Ozturk *et al*., 2017).

TELOMERASE AND AGING

In eukaryotic chromosomes, there are some specialized sequences of DNA present called telomeres. They are located at the ends of chromosomes. In humans, they are composed of the TTAGGG sequence, which is tandemly repeated for up to 15 kilobases at birth. They are formed by an enzyme called telomerase, which is a ribonucleoprotein reverse transcriptase enzyme whose role is to maintain the chromosome's length. The function of telomere sequences is to stabilize the ends of a chromosome, which is accomplished by binding it with a protein. This binding to proteins helps to prevent the telomere sequences from being recognized by the nuclease enzymes. Loss of telomerase causes the termini of the chromosome to attrite, which can lead to subsequent fusion, translocation, rearrangement, or breakage within the DNA domain.

To gerontologists, the telomerase enzymes, whose role is to stabilize the termini of the chromosome, is of considerable interest. This is because of its expression, which is considered to be essential for cellular immortalization, and cellular aging is the consequence of its absence. In 1989, telomerase activity in human cells (in crude HeLa cells) was first reported by Morin (Morin, 1989). Those cells which have unlimited proliferative life span contain telomerase in its active form, e.g., it is active in germline and embryonic stem cells. It is not expressed or inactive in tissues, which have limited proliferated life span, e.g., somatic cells. Cells with limited life span have decreased telomere length every time the cell divides, while cells immortal in nature have defined telomere length that rejuvenates itself after cell division event. This proves that there is a link between cell mortality, the stability of chromosome, and telomerase presence. Actively dividing cells stop dividing after telomere sequence has shortened to a specific length. After a woman conceives, the shortening of the telomeres starts with the differentiation of cells. Telomerase in some of the cells, although, is inactivated, but the activity of telomerase can easily be observed after birth. So, this shortening of telomeres and the absence of telomerase in later life stages can be considered as a molecular clock that activates the aging of cells that become incapable of dividing.

Tests were performed to observe the effect of telomerase and its relation with cellular division and aging. Vectors that encoded subunit of human telomerase were inserted in somatic cells that had to age (Katayama *et al*., 2015; Ramunas *et al*., 2015). Results were exciting as these cells divided indefinitely and remained youthful aged. In other studies, Human fibroblasts of the dermal layer were immortalized when telomerase was inserted into them in-vitro conditions (Funk *et al*., 2000; Smith *et al*., 2013; Ramunas *et al*., 2015). The resultant cells also showed a reversal of characteristics developed as a result of aging. So, consequences, both biological and medical-related to the expression of telomerase, are of high importance.

GENE THERAPY AS A TREATMENT TO AGING IN MODEL SYSTEMS

On various experimental models, studies have been performed to indicate that life span can be extended by genetic intervention. The various model system includes nematodes, *Drosophila melanogaster*, mice, and yeast and now humans as well. The results of different experiments on mice and *Drosophila melanogaster* model systems are briefly discussed:

ANTI-AGING GENE THERAPY IN *DROSOPHILA MELANOGASTER*

Due to rapid generation time and a comparatively short life span of about 60-80 days, *Drosophila melanogaster* is an efficient model system for gerontology research. According to the latest updates of "Gene Database (GenAge)," 108 out of 170 genes are linked in increasing the life-span of this model organism (Tacutu *et al*., 2018), which are briefly mentioned below.

VIA MUTATION

Wang *et al*. demonstrated in his study that the mutation in the **PUC (puckered) gene** led to the loss of its function, which thereby increased the life span (Wang *et al*., 2003). In the following year, the mutated **sun (Stunted) gene** showed an increase in the life span (Cvejic *et al*., 2004). When dominant-negative versions of **p53 (CG33336-PA)** genes were expressed in neurons of adult flies, it increased the resistance to genotoxicity stress and increased the life span by 32% in males and 58% in females (Bauer *et al*., 2005). Also, both heterozygous male and female flies with mutated **ILK (Integrin-linked kinase)** showed an increased life span with a 37-60% increase in females and 56-63% in males (Nishimura *et al*., 2014). Mutations in dwarf females in **INR (Insulin-like 1 receptor) gene** extended life span up to 85%, and in dwarf males, the life span was also increased (Tatar *et al*., 2001). When some of the male genetically identical siblings heterozygotes were mutated for **KEAP-1 (CG3962 gene product from transcript CG3962-RA) gene,** the life span was increased significantly about 8-10% while the female

heterozygotes showed no difference (Sykiotis *et al*., 2008). Loss of **14-3-3e (CG31196 gene product from transcript CG31196-RA)** increased growth repression and the life span. When the expression of **14-3-3e** was increased, it reversed the FOXO-induced effects of growth (Nielsen *et al*., 2008). While no effect was seen in adipose tissues. The average male life span was increased by 25%, and the female life span was increased by 49%. **Mutant alpha-man-1 (Alpha Mannosidase I)** extended the mean life span in both sexes, which is about 60% (Liu *et al*., 2009). When the mutant was outcrossed, a 22% life span increase in females and a 38% life span increase in males was observed. **Mutant bam (bag of marbles)** *Drosophila melanogaster* showed that female and male life span was increased by 50% and 27.8%, respectively (Flatt *et al*., 2008). Loss-of-function mutation in **ORCO (Odorant receptor co-receptor) gene (ORCO heterozygotes)** and **COQ 2 (Coenzyme Q biosynthesis protein 2)** also increased life span. Female **Or83b2 of (orco gene mutant)** mutated flies showed a 56% and 30% increase in median and maximum life span, respectively (Bodnar *et al*., 1998; Fossel, 1998). The lifespan of males was also extending but to a smaller degree. The dominant **ovoD1 allele of the OVO (CG6824-PA) gene** resulted in almost 50% of the increase in female life span, but it cannot revert or prevent life extension caused by **CHICO** (Sgro *et al*., 1999). **DNC (dunce)** and **ECR (Ecdysone receptor) genes** mutated (heterozygotes) *Drosophila melanogaster* showed an extended life span. In the case of the **DNC gene**, the extension was about 70%, and in the case of **ECR,** a 40 to 50% increase was observed (Tatar *et al*., 2003; Tong *et al*., 2007). **L(3)DTS3 (lethal (3) DTS3)** female mutants also showed a 42% increased mean life span (Simon *et al*., 2003). While the mean life span of both the sexes increased by more than 30% due to the **mutant EDEM1 (CG3810 gene)** product from the transcript (CG3810-RC) gene (Liu *et al*., 2009). Heterozygous **E(z) (Enhancer of zeste)** mutant flies also showed an increased life span (Siebold *et al*., 2010). Similarly, ESC (extra sex combs) males heterozygotes showed an increase in the life span for the dominant-negative mutation (Siebold *et al*., 2010). Mutation in **LNK (CG17367) gene** product from transcript CG17367-RC) gene displayed resistance to starvation and oxidative stress (Song *et al*., 2010). The insertion of p-element in the **MUB (mushroom-body expressed) gene** extended the life span of mutants of both sexes. While insertion of p-element in **ESG (escargot)** and **CROL (crooked legs)** displayed an extension in the life span of males only (Magwire *et al*., 2010). **MYS (myospheroid)** also showed an increased life span when mutated. Mutation in **CAR (carnation) gene** also increased the life span (Simonsen *et al*., 2007). In 2008 another experiment was done in which **SNZ (sorting nexin lazarus) gene** was mutated that led in prolongation of life span (Suh *et al*., 2008). The maximum life span was observed to be 66% higher, while the median life span was approximately 85% higher in females and approximately 72% in males. In 2014, another researcher Waterson *et al*., observed that on the mutation of **PPK28 (pickpocket 28) gene** maximum and mean life span extension in *Drosophila melanogaster*, which was 25% and 25-44% (Waterson *et al*., 2014). The **Rpd3 (CG7471-PA)** was mutated, which led to the extension of life span by 33% and 52% in males and females flies, respectively (Rogina *et al*., 2002). A dominant-negative mutation in the **S6K (RPS6-p70-protein kinase) gene** also led to the prolongation of the life span of the model organism. Same kind of genetic modification called "dominant negative mutation" in **TOR (Target of rapamycin) gene** that is involved in cell growth and size was done (Kapahi *et al*., 2004). It was observed to be successful in the extension of life span.

VIA KNOCKOUT

Knock out to a putative COX assembly factor gene called **SURF1 (surfeit gene 1) gene** increased the maximum life span by 20-30% (Zordan *et al*., 2006). Knockout of the **BMCP gene** increased life span while knockout of **EGM (enigma)** along with increasing life span also increased resistance to oxidative stress (Sánchez-Blanco *et al*., 2006). A 48% increase in life span was observed by knockout of **CHICO (Insulin receptor substrate-1) gene** in homozygotes and 36% in heterozygotes (Clancy *et al*., 2001).

VIA RNA INTERFERENCE

Post-developmental al RNA interference increased the life span of **BABO (baboon) gene** by 16% but only in muscle, and no effect was observed in adipose tissues while the post-developmental al RNA interference in **GLYP (Glycogen phosphorylase)** increased the life span by 17.1% (Bai *et al*., 2013). Neuron-specific post-developmental RNA interference in **GLYS (Glycogen Synthase)** in adult male flies extended the life span significantly. A 10% increase in median life span was observed, and no such extension was observed in females (Sinadinos *et al*., 2014). As far as **L(3)NEO18 gene** is concerned, RNA interference when done during adulthood and development stage in the whole organism increased the life span by 14-18%, but the increase was about 8-24% when done in neurons. Results of males varied, but mostly an 8-18% increase was observed (Copeland *et al*., 2009). Knockdown of **KRA/ECP (krasavietz) gene** in males increased the life span by 16-21%, and in females, the increase was 18-25% (Wang *et al*., 2014 a). Muscle-specific RNA interference of **ND75 (NADH: ubiquinone reductase 75kD subunit precursor)** preserved the ability of locomotion and increased the life span by 19% (Owusu-Ansah *et al*., 2013).

RNA interference in **DAW (dawdle) gene**, when done in the whole body, brought about a 35% increase in life span (Bai *et al*., 2013). RNA interference, when carried out in **CG17856 (CG17856 gene product from transcript CG17856-RA)**, extended the mean life span of females by 13-18%, but in males, the results of these experiments are variable (Copeland *et al*., 2009). The result for **CG18809 (CG18809 gene product from transcript CG18809-RA)** on RNAi exposure increased the mean life span of females by 8-19% and in neurons resulted in a 6-24% increase in females while results varied for males (Copeland *et al*., 2009). Lack of inhibition of **CG2789/dTSPO** either through RNA interference or pharmacologically, extended the median as well as maximum life span in male flies by 27% and 15%, respectively (Lin et al., 2014 a). RNA interference **CG5389 (CG5389 gene product from transcript CG5389-RA)** started right from the development increased life span in both sexes; almost 3-11% (Copeland *et al*., 2009) and RNAi of **CG9172 (CG9172 gene product from transcript CG9172-RA)** during development or adulthood extended the mean life span by 4-12% in female flies while a 46% increase was observed when done in adult neurons only. The effect varies in males (Copeland *et al*., 2009). **RPI (Ribose-5-phosphate isomerase) gene** expression was reduced through RNA interference in 2012, which increased the average life span by 38% (Wang *et al*., 2012). Next year in 2013, Post-developmental RNA interference in **SMOX (Smad on X) gene** increased the mean life span by 10% (Bai *et al*., 2013). The same intervention was experimentally done for **TSP42EF (Tetraspanin 42Ef) gene** that showed an 18.2% median life span higher than wild type (Bai *et al*., 2013). Knockdown of the "**RDGA (retinal degeneration A)**" gene by RNA interference as genetic modification in flies led in the extension of mean life span by 44% according to the observation of (Lin *et al*., 2014).

VIA OVEREXPRESSION

Mockett *et al.* observed that overexpression of the **TRXR-1 (Thioredoxin reductase-1) gene**, associated with a role of redox regulation and oxidative defense, in transgenic flies, resulted in the extension of life span (Mockett *et al*., 1999). In 2003, an experiment was conducted in which **RDH (CG14975-PA) gene** was overexpressed showed a 6-8% higher average life span than the wild types (Landis *et al*., 2003). In the same year, two similar experiments were performed, **SUG (sugarbabe) gene** was overexpressed that extended the average life span with 5-9% while the other gene named **VHASFD (Vacuolar H+-ATPase SFD subunit)** also showed 5-10% extension (Landis *et al*., 2003). Next year in 2004, the same genetic intervention in **TSC1 (CG6147-PA Tuberous sclerosis complex genes 1) gene** showed an extension (Zordan *et al*., 2006). Overexpression of the **UCP2 gene**, namely as **uncoupling protein 2 (mitochondrial, proton carrier) gene**, also increased the life span by 10-30% (Fridell *et al*., 2005). The mean life span became 18% higher when a gene named pink **(PTEN-induced putative kinase 1)** is overexpressed. According to Todd and Staveley, overexpression of **alpha-synuclein** led in a 40% enhancement of effect on the life span as well (Tong *et al*., 2007). Overexpression of **CBS (Cystathionine beta-synthase) gene** increased the mean as well as the maximum life span of the female by 12-43% and 10%, respectively. While in males, only a 7% increase was observed. Life span increased by overexpression of **CBS** in neuronal cells only (Kabil *et al*., 2011). Similarly, overexpression of **Atg1 (Autophagy-specific gene 1)** in neuronal cells increased the median as well as the maximum life span by 25%. Furthermore, overexpression of **Atg2 (Autophagy-specific gene 2)** increased the life span by 28% (Simonsen *et al*., 2008). Overexpression of **IMP-L2 (Ecdysone-inducible gene L2)** was observed to have increased resistance to oxidative stress. Moreover, the median life span was observed to increase by 23%. Moreover, overexpression of **Imp-L2** by using **hsGAL4** driver increased the female median life span by up to 15% while there was no effect on maximal life span by using this driver (Alic *et al*., 2011). Overexpression of the **CAT (catalase) gene** resulted in a one-third higher life span (Orr *et al*., 1994), while **CCT1** increased mean life up to 8%. (Landis *et al*., 2003). Neuronal overexpression of **JAFRAC1 (Thioredoxin peroxidase 1)** also increased both mean and maximal life span of female 26% and 22% respectively and male by 29% and 26% respectively (Lee *et al*., 2009). When **CG11165** was overexpressed, increased median (54%) and maximum (17%) life span (Merino *et al*., 2015) while overexpression of **CG13890** in flies' increases life span up to 31% (Lee *et al*., 2012). Overexpression of the **CHER (cheerio) gene** resulted in a 7-9% increase in mean life span (Ehmann *et al*., 1997). **HSP27 (Heat shock protein 27) gene** overexpression extended resistance against stress and the mean life span by 30% (Wang *et al*., 2004). Overexpression of **HSP68 (Heat shock protein 68)** and **HSP70 (Heat shock protein) genes** also increased the life span (Tatar *et al*., 1997; Wang *et al*., 2003). Life span also improved when **MTH (Methuselah)** was overexpressed in the insulin-producing cells of the brain, and stress resistance was observed. The mean life was increased by 12-16% in males and 14-21% in females (Gimenez *et al*., 2013). **GIG (gigas)**, **FOXO (Forkhead box, sub-group O)**, **FWD (four wheel drive), GCLM** (**Glutamate-cysteine ligase modifier subunit)** genes also increased the life span when overexpressed, and while for **GCLM** it was 24% (Landis *et al*., 2003; Hwangbo *et al*., 2004; Kapahi *et al*., 2004). In the case of **FWD**, it was 7-9% (Orr *et al*., 2005). In the nervous system, a significant extension in life span was reported as a result of overexpression of **GADD45 (CG11086 gene product from transcript CG11086-RA) gene** (Plyusnina *et al*., 2011). Overexpression of **Ef1alpha48D (Elongation factor**

148D) increased life span by 18-41% (Shepherd *et al*., 1989). In female transgenic *Drosophila melanogaster*, the overexpression of the **FH (frataxin homolog)** gene in the mitochondria increased resistance to oxidative stress as well as antioxidant capability (Runko *et al*., 2008). Along with this, it also increased the median life span by up to 35%, and the maximum life span up to 28%. Upregulation of **Park (parkin)**, in adult *Drosophila melanogaster*, increased both mean and maximum life span without affecting reproductive output or intake of food and physical performance (Rana *et al*., 2013). Although the effect was smaller in males and larger in female's life span up to 28%. While the upregulation of **GCLC (Glutamate-cysteine ligase catalytic subunit) gene** surged the average and maximal life span by 50% (Orr *et al*., 2005). **ILP6 (Insulin-like peptide 6)**, when overexpressed in the abdominal fat body, increased the life span of female *Drosophila melanogaster* but if on a low yeast diet. While overexpression of the same gene in the head fat body increased life span if maintained on a high yeast diet. No effect was seen in males. The increase in the life span of females was about 15.6% (Bai *et al*., 2012). Both **HSC70-3 (Heat shock protein cognate 3)** and **GSTS1 (Glutathione S transferase S1)** increased average female life span by 27% and 33% respectively (Simonsen *et al*., 2008) but **HEBE (hebe gene product from transcript hebe-RD)** and **MAGU (magu gene product from transcript magu –RD)** gene when overexpressed not only increased the life span by 5-30% but also modulated late-age female fecundity (Li *et al*., 2009). Moreover, the average life span of the male was 24% increased. The result of the overexpression of **NF1 (Neurofibromin 1)** was an increase in mitochondrial respiration reduced the production of reactive oxygen species. It also affected the life span by increasing mean life span by 68% in females and 49% in males while maximized longevity by 52% and 38% with improved reproductive fitness, respectively (Tong *et al*., 2007). Overexpression of the **PCMT (Protein-L-isoaspartate (D-aspartate) O-methyltransferase)** increased the life span only by 32-39% (Chavous *et al*., 2001) and overexpressed **MT2 (DNA methyltransferase-2)** also increased life span likewise (Lin *et al*., 2005). Similarly, when the **NAAM (Naam gene product from transcript Naam-RA)** gene was overexpressed life span increased by up to 30%. This increase was dependent on **SIR2** and was not observed in **SIR2 mutants** (Balan *et al*., 2008). Increased stress resistance was observed along with a 30% increased life span by overexpression of **HSP26 (Heat shock protein 26)** (Wang *et al*., 2004). During larval periods overexpressed **MEN (malic enzyme)** extended the maximum life span in *Drosophila melanogaster*, which was 39% in females and 24% in males (Kim *et al*., 2015). Overexpression of **MTF1 (Metal response element-binding Transcription Factor-1) gene, MYO (myoglianin) gene**, and **INAE (inactivation no after potential E) gene** increased life span depending upon calibrated conditions (Demontis *et al*., 2014; Lin *et al*., 2014 b). In the nervous system, overexpression of **EIP71CD (Ecdysone-induced protein 28/29kD)** extended life span by 70% (Ruan *et al*., 2002). Its overexpression also extended resistance against the oxidative stress and delayed the onset of senescence-induced decline in reproductive activity. Overexpression of **FABP (fatty acid-binding protein)** ameliorated the average life span by 81% (Lee *et al*., 2012).

In 2007, **TRXT (Thioredoxin T) gene** was overexpressed that led to a 15% extension in the average life span (Umeda-Kameyama *et al*., 2007). Similarly, the same kind of genetic manipulation was done for **PKA-C1 (cAMP-dependent protein kinase 1) gene,** which on its overexpression, increased the life span by 30% (Todd *et al*., 2012). Another gene, "**POSH (Plenty of SH3s)**," was also overexpressed (Seong *et al*., 2001), which led in 14/% extension in the mean life span of adult flies. In 2008, **ZW (Zwischenferment) gene** was targeted for genetic modification, and thus its overexpression showed the same results. The average life span observed was about 38% (Legan *et al*., 2008). In 2009, the average life span was observed to be 30% higher by overexpressing the **PRX5 (Peroxiredoxin 5) gene** (Radyuk *et al*., 2009). **Thor (CG8846 gene product from transcript CG8846-RA) gene** was overexpressed, which showed a 22% increase (Zid *et al*., 2009) and extended the median and maximum life span by 20% and 15.8% respectively (Demontis *et al*., 2010). **Takeout gene "To"** also showed prolongation in the life span. The maximum life span in males and females was 13% and 23%, while the median longevity was up to 18% and 26%, respectively (Bauer *et al*., 2010). The same genetic intervention was applied on **PTEN (CG5671 gene product from transcript CG5671-RB)** gene as well as in **4E-BP** in muscles, which led to prolongation of maximum and median life span by 7.7% and 12.7%, respectively (Demontis *et al*., 2010). In 2011, another gene named **SPARGEL** was modified that extended the life span of the female model organism by 33% (median) and 37% (maximum), respectively (Rera *et al*., 2011). In 2014, the overexpression of the **SNF1A (SNF1A/AMP-activated protein kinase) gene** extended the median life span by 20% (Ulgherait *et al*., 2014).

VIA DELETION

In **GR63A (Gustatory receptor 63a)**, loss of function in female flies increased life span by up to 30%. Moreover, it increased resistance to some of the environmental stresses and increased fat deposition as well, while no effect of the same gene deletion was observed in males (Poon *et al*., 2010). Similarly, the deletion of **ILP2 (insulin-related peptide)** increased the maximum life span of females and males up to 40% and 27%, respectively,

while median female and male life span were increased up to 33.5% and 10.5%, respectively (Broughton *et al*., 2005). This also increased resistance to oxidative and starvation stressors.

ANTI-AGING GENE THERAPY IN MOUSE MODELS

Different genetic manipulations were made out, including deletions, knock out, overexpression, and replacements of genes to increase the life span of these rodent models. According to the "Gene Database (GenAge)," there are a total of 136 genes that are involved in aging, out of which 50 genes identified that were associated with an increase in the longevity of the rodents (Tacutu *et al*., 2018) which are highlighted below:

VIA MUTATION

Replacement of **Proline-1195** of insulin receptor with **Leucine** created a homologous murine model. The survival of mutant female mice was 33.3% longer than wild-type female mice.

On the other hand, it was 18.2% longer for the mutant male than the wild type (Baba *et al*., 2005). According to the observation of (Xu *et al*., 2014), the mutation in the **IGF1R (Insulin-like growth factor 1 receptor) gene** showed an 11% increase in a life span of IGF-1R+/- mutant female mice. Moreover, the same phenomenon of mutation was applied in the **MYC gene,** which extensively increased the life span from 10 to 20% (Hofmann *et al*., 2015). In other cases, mice that lacked the **TRPV1 gene** were identified to be lived longer than wild ones when their gene was mutated (Riera *et al*., 2014).

VIA KNOCK OUT AND KNOCK IN

Longevity was also achieved in *Mus musculus* by a knock in or knock out of the genes. In the case of Yan *et al*., the knockout of the **Adcy5 gene** that codes for a protein adenylate cyclase-5 responsible for the synthesis of Cyclic-AMP, increased 30 % median life span, and 12 % maximal life span. This is due to the increase in mice resistance to cardiac stress (Yan *et al*., 2007). Other than that, knock out of **AGTR1A (Angiotensin II receptor, type 1a) gene** has shown an extension in the median as well as in maximal life span of 26 and 24%, respectively (Benigni *et al*., 2009). Another gene called **BAX (Bcl 2-associated X protein) gene** associated with apoptosis function once knock out had also extended the life span significantly (Perez *et al*., 2007). **CTF1 (cardiotrophin-1) gene** knock out accomplished by López-Andrés *et al*. extended the average life span by 18 % in mice (López-Andrés *et al*., 2013). Knock out of the **DGAT1 (diacylglycerol O-acyltransferase-1) gene** in female mice have an increased life span of about 23 % (Streeper *et al*., 2012). Moreover, **GHR (Growth hormone receptor) gene** knock out increased the life span by 40% in males and by 21% in female mice (Coschigano *et al*., 2003). Similar genes such as **GHRH (growth hormone-releasing-hormone)** and **GHRHR (Growth hormone-releasing-hormone receptor)** extended the life span by 46% and 20%, respectively (Flurkey *et al*., 2001; Sun *et al*., 2013). **GPX4 (Glutathione peroxidase 4) gene** knock out resulted in a 7% extension in median life span (Ran *et al*., 2007). Gene named "**glutathione S-transferase, alpha-4 (GSTA4)**" disruption in mice extends the average life span by 13% (Singh *et al*., 2010). **IKBKB (inhibitor of kappa B kinase beta) gene** knock out in the brain increased the average life span of mice by 23% (Zhang *et al*., 2013). Similarly, Liu *et al*. observed a 15% to 30% increase in the life span of heterozygous mice (Liu *et al*., 2005). I**gf1r (Insulin-like growth factor 1 receptor)** knock out increased the average life span of female mice with 33%, and for males, it was 16% (Holzenberger *et al*., 2003). The same gene in the brain was knock out, which led to the extension of life span by 40% (Kappeler *et al*., 2008). Knock out of both **IRS1 (insulin receptor substrate 1)** and **IRS2 (insulin receptor substrate 1) gene** in mice augmented life span by 18% (Taguchi *et al*., 2007; Selman *et al*., 2008) and **MIF (macrophage migration inhibitory factor) gene** have also shown a significant extension in life span by 16% (Harper *et al*., 2010). In accordance with the results published by Migliaccio *et al*., **SHC (SRC homology 2 domain-containing) transforming protein 1) gene** knock out extended the life span with 30% (Migliaccio *et al*., 1999). Similarly, the **PROP-1 gene** also induced an extension in the life span (Brownborg *et al*., 1996). **PRKAR2b gene** also shown a 14% prolongation in median life span when it was knocked out (Enns *et al*., 2009). Another protein-coding gene called **SURF-1 gene** knock out also brought a 20% extension (Dell'agnello *et al*., 2007). Canaan *et al*. observed that **FAT10 (Ubd)** knock out resulted in a life span prolongation by 20% (Canaan *et al*., 2014). The same genetic manipulation in the **TERT gene** also was another approach for the extension of life span in these organisms (Jaskelioff *et al*., 2011). According to Takahashi *et al*., in 2014, the transgenic mice deficient of **CLK-1** gene showed an extension in the life span (Takahashi *et al*., 2014). In the male mouse, 20% and 23% extension observed in maximum and median life span while in female mice, it was 12% and 14%.

VIA GENETIC REDUCTION

Genetic reduction in **Akt1 (thymoma viral proto-oncogene 1) gene** showed prolongation in the life span of Haplo-insufficient mice. When it was compared to wild type, the mean life span was 15 % higher in females and 8% in males (Nojima *et al*., 2013). Similarly, the genetic reduction in the **mTOR gene** brought a 20% life extension (Wu *et al*., 2013).

VIA OVEREXPRESSION

One of the reasons for aging is a decline in the function of an organ due to damage caused by reactive oxygen species (ROS) in accordance with the free radical theory of aging. Reactive oxygen species are those chemical compounds that are a normal part of metabolism, e.g., H_2O_2 groups of enzymes called catalase enzyme are present within our body to protect the body from the damage caused by H_2O_2 (Schriner *et al*., 2006). **Cat (catalase) gene** overexpression in mitochondria extended life span by 20% (Schriner *et al*., 2005). The same gene was overexpressed in skeletal and cardiac muscles, which led to prolongation of maximum and median life span by 17-21% (Cutler, 2005). Overexpression of **Atg5 (autophagy-related 5) gene** increased the life span by 17.2% (Pyo *et al*., 2013). This genetic intervention made the mice show anti-aging phenotypes, improved motor functions, and increased insulin sensitivity. Similarly, **ADRA1A (adrenergic receptor, alpha 1a) gene** in transgenic mice has increased the maximum life span of 8% and the median life span of 10% (Doze *et al*., 2011). Another gene called **FGF21 (fibroblast growth factor 21) gene** in hepatocytes extended the average life span by 36% and maximum life span by 16% (Zhang *et al*., 2012). **GDF15 gene, named as growth differentiation factor 15,** showed the same results (Wang et al., 2014 b). It extended the mean life span of mice that were female by 43%, respectively. **MT1 gene** was also overexpressed, which resulted in a 14% life span extension (Yang *et al*., 2006). Luca *et al*. observed prolongation in life span by overexpressing the **NUDT1 gene** (Luca *et al*., 2013). This extension was 16% and 22% in the median and maximum life span, respectively. The same method of genetic manipulation **Plau** was done for the **PCK-1 gene** that led to the prolongation of the life span of mice (Hakimi *et al*., 2007). Conti *et al*. also observed the life extension by the same means associated with the **UCP2 gene**, which was 12 % in both female and male mice (Conti *et al*., 2006). Approximately 35% higher maximum and median life span observed for the **TXN1 gene** (Mitsui *et al*., 2002). **TERT gene** is a telomerase reverse transcriptase gene associated with telomere elongation. Its overexpression increased life span; the extension observed was 9-50% higher in both sexes (Tomas-Loba et al., 2008).

VIA DELETIONS

The gene called **CDKN1A (Cyclin-dependent kinase inhibitor 1A) gene** a cyclin-dependent kinase inhibitor of CDK4 and CDK2, also known as p21. The deletion of CDKN1A has prolonged the life span significantly and improved the stem cell functions and dysfunctional telomeres without accelerating the formation of cancer (Choudhury *et al*., 2007). The deletion of the **EPS8 gene** that stands for "epidermal growth factor receptor pathway substrate 8" led in prolongation of maximum, median and average life span with 9%, 26%, and 37%, respectively. These mice, due to impaired fat absorption, appear to be caloric resistant (Tocchetti *et al*., 2010). The **CEBPA (CCAAT/enhancer-binding protein (C/EBP), alpha) gene** encodes for a protein that acts as a transcription factor in the metabolism of fats. Replacement of the **CEBPA gene** with another gene called **Cebpb (CCAAT/enhancer-binding protein (C/EBP), beta)** extended the life span by about 20% (Chiu *et al*., 2004). The polyglutamine stretch was deleted in the **Huntingtin gene (Htt)**, which thereby increased the maximum and median life span by 17% and 18%, respectively (Zheng *et al*., 2010). The **Insulin receptor gene (INSR)** is associated with the signal transduction of insulin. The deletion of this gene in adipose tissues prolonged the life span (Blüher *et al*., 2003). Similarly, **gene KCNA3** also showed a 22% extension (Tucker *et al*., 2008). The same genetic manipulation was applied for **POU1F1, RPS6KB1, Serpine1, PAPPA, and SLC13A1 gene,** respectively. **POU1F1 gene** showed a 40% extension in maximum and average life span (Flurkey *et al*., 2001), **RPS6KB1** showed 19% prolongation in median female life span (Selman *et al*., 2009), **PAPPA gene** showed 30-40% extension (Conover *et al*., 2007) while **SLC13A1 gene** showed approximately 25% extension in maximum (male only) and median life span respectively (Markovich *et al*., 2011). **SERPIN 1** inhibition through plasminogen activator inhibitor-1 in the Klotho-deficient (*kl/kl*) mice, four times increased the median life span (Eren *et al*., 2014) whereas **BRCA1 gene** deletion led in extension respectively (Cao *et al*., 2009).

VIA TELOMERASE GENE THERAPY

Studies on aging are conducted in order to extend life or a disease-free life. The relationship between aging and telomerase is known to exist for a long time, and such a relationship is exploited to conducted genetic experimentations on mouse models to ameliorate life span and prevent the onset of aging-associated diseases.

Therapies affecting the length of telomere are expected to affect the accumulation of dysfunctional and damage telomeres with ageing. It is considered as a prime reason for DNA damage caused by aging both in humans and mice that in turn aggravates improper activity of telomerase (Blasco *et al*., 1997; Herrera *et al*., 1999; Mitchell *et al*., 1999; Vulliamy *et al*., 2001; Flores *et al*., 2005; García-Cao *et al*., 2006; Armanios *et al*., 2007; Tsakiri *et al*., 2007; Schoeftner *et al*., 2009).

Activation of telomerase is considered a useful trick to immortalize tissues and avoid diseases related to the premature shortening of the telomere (Bernardes de Jesus *et al*., 2011; Jaskelioff *et al*., 2011). Surprisingly, although human telomeres are shorter than mice telomeres, drastic shortening occurs in mouse telomeres at old ages and as a result decreases life span (Garcia-Cao *et al*., 2006; Flores *et al*., 2008). This fact is further supported by the delayed aging in mice that are resistant to cancer through the activation of telomerase (Tomás-Loba *et al*., 2008). However, except for mice that are genetically engineered to be resistant against cancer, increased telomerase expression is linked with a higher susceptibility to the development of cancer both in human and in mice (Gonzalez-Suarez *et al*., 2001; Artandi *et al*., 2002; Canela *et al*., 2004; McKay *et al*., 2008; Rafnar *et al*., 2009).

According to some studies, an increase in the expression of **TERT** in old/adult mice increases life span with no increased cancer risk (Armanios *et al*., 2007; Tsakiri *et al*., 2007). Overexpression of telomerase led to an extension in the life span of 24% in 1-year-old mice, whereas it was 13 % in 2-year-old (Bernardes de Jesus *et al*., 2012). Interventions in **TERT,** particularly by vectors of (AAV9-mTERT) adeno-associated vectors, reactivated the activity of telomerase, especially in the mouse of age one or two years and positively affected the health of these organisms. These effects included a delay in osteoporosis, improvement in metabolic function, and improved coordination in nerves and muscles. This experiment might be helpful to humans as AAV9-TERT successfully reactivated telomerase efficiently in the lungs of mice. By adopting similar interventions could be useful for the treatment of pulmonary fibrosis in which mutation in the telomerase enzyme simultaneously shortens the telomere length of lung cells resulting in premature senescence (Armanios *et al*., 2007; Tsakiri *et al*., 2007).

Through this experiment, we can conclude that anti-aging gene interventions can be applied to adult and young mammals. With the help of telomerase gene therapy, delay and repair of DNA damage caused by telomere can be cured. This can lead to an increased life span of organisms (Bernardes de Jesus *et al*., 2012; Boccardi *et al*., 2012).

GENE THERAPY IN OTHER SPECIES

According to "the Aging Gene Database," there is a total of 2,115 genes that are associated with aging (Tacutu *et al*., 2018). In *Caenorhabditis briggsae*, only one gene is involved in the extension of life. **CBR-DAF2,** when mutated, increased the lifespan by up to 30-40% (Inoue *et al*., 2007). In *Caenorhabditis elegans*, 570 out of 838 genes increased lifespan. The top life-extending gene is **age-1** (Tacutu *et al*., 2018). Mutation in **age-1** increased the mean lifespan by 65% (Johnson, 1990). Only the **Csnk1e gene** of *Mesocricetus auratus* was responsible for extension in the life span. A mutation in **Csnk1e** increased the lifespan by 14-16%, along with an increase of metabolic rate (Oklejewicz *et al*., 2002). In *Podospora anserine*, only three genes gave a positive result for lifespan extension. **PODANSg7134** is the top life-extending gene of *Podospora anserine* (Tacutu *et al*., 2018). On the other hand, 270 out of 883 genes of *Saccharomyces cerevisiae* increased the lifespan, and the top life-extending gene was **SIR2**. Similarly, in *Schizosaccharomyces pombe***,** 26 out of 31 genes are involved in lifespan extension. The top life-extending gene known till now is the **SPBP4H10.16c gene** (Tacutu *et al*., 2018).

GENE THERAPY IN HUMAN CELL LINES

According to the "Gene Database (GenAge)," there is a total of 307 genes associated with aging. Scientists are still working on those genes that are associated with an extension of human life (Tacutu *et al*., 2018). The relation of telomerase with the extension of life span in healthy human diploid fibroblast cells was determined by masking the activity of telomerase and expressing **hTERT** through retroviral vector pBabe (Smith *et al*., 2013). Results showed that this retroviral mediated hTERT expression led to the functional activity of telomerase in healthy aging cells of humans. Moreover, in vivo telomerase activity, reconstitution led to an extension in telomeric DNA length and an increase in cellular life span. This indicates that one of the factors in the determination of the replicative life span of human cells is telomere length, which gives a lucrative proof in support of the telomerase hypothesis (Vaziri *et al*., 1998). In telomerase-induced extended life span human fibroblasts cells (**TIELF**), it is notable that the telomeric DNA length was not merely maintained but extended. After this experiment, similar results by Bodnar *et al*. (Bodnar *et al*., 1998) were reported in which the older cells which had spent 80% of their life were used, demonstrating that even in old cells aging can be prevented. Similar approaches may also be utilized as a remedy against cancer and other aging-related diseases

CONCLUSION

Gene therapy for anti-aging is far different from usual gene therapies in which diseases are cured because only one gene or protein is targeted. Longevity and aging both are polygenic traits, and the total number of genes involved in these processes is not yet determined. Moreover, the genes identified in model systems either need to be switched off or their transcription highly reduced in order to increase life span. The genes involved to increase the life span also need to be further analyzed, or otherwise incomplete genetic experimentation may disrupt the vital metabolic and physiological functions. Gene therapy for anti-aging is still in its infant stages, and development has to be done to make it 100% successful. During performing these experiments, ethical issues should also be kept in mind.

REFERENCES

Ahmed, M. S., S. Ikram, N. Bibi and A. Mir (2018). Hutchinson–Gilford progeria syndrome: a premature aging disease. *Molecular neurobiology*, 55(5): 4417–4427.

Alic, N., M. P. Hoddinott, G. Vinti and L. Partridge (2011). Lifespan extension by increased expression of the Drosophila homologue of the IGFBP7 tumour suppressor. *Aging cell*, 10(1): 137–147.

Amaro-Ortiz, A., B. Yan and A. J. D' Orazio (2014). Ultraviolet Radiation, Aging and the Skin: Prevention of Damage by Topical cAMP Manipulation. *Molecules*, 19(5): 6202–6219.

Armanios, M. Y., J. J. Chen, J. D. Cogan, J. K. Alder, R. G. Ingersoll, C. Markin, W. E. Lawson, M. Xie, I. Vulto, J. A. Phillips, P. M. Lansdorp, C. W. Greider and J. E. Loyd (2007). Telomerase mutations in families with idiopathic pulmonary fibrosis. *New England Journal of Medicine*, 356(13): 1317–1326.

Artandi, S. E., S. Alson, M.K. Tietze, N. E. Sharpless, S. Ye, R.A. Greenberg, D. H. Castrillon, J. W. Horner, S. R. Weiler, R. D. Carrasco and R.A. DePinho (2002). Constitutive telomerase expression promotes mammary carcinomas in aging mice. *Proceedings of the National Academy of Sciences*, 99(12): 8191–8196.

Aunan, J. R., W.C. Cho and K. Søreide (2017). The biology of aging and cancer: a brief overview of shared and divergent molecular hallmarks. *Aging and disease*, 8(5): 628.

Baba, T., T. Shimizu, Y. Suzuki, M. Ogawara, K. Isono, H. Koseki, H. Kurosawa and T. Shirasawa (2005). Estrogen, insulin, and dietary signals cooperatively regulate longevity signals to enhance resistance to oxidative stress in mice. *Journal of Biological Chemistry*, 280(16): 16417–16426.

Bai, H., P. Kang and M. Tatar (2012). Drosophila insulin-like peptide-6 (dilp6) expression from fat body extends lifespan and represses secretion of Drosophila insulin-like peptide-2 from the brain. *Aging cell*, 11(6): 978–985.

Bai, H., P. Kang, A. M. Hernandez and M. Tatar (2013). Activin signaling targeted by insulin/dFOXO regulates aging and muscle proteostasis in Drosophila. *PLoS genetics*, 9(11): e1003941.

Balan, V., G. S. Miller, L. Kaplun, K. Balan, Z. Z. Chong, F. Li, A. Kaplun, M. F. A. VanBerkum, R. Arking and D. C Freeman (2008). Life span extension and neuronal cell protection by Drosophila nicotinamidase. *Journal of Biological Chemistry*, 283(41): 27810–27819.

Bauer, J., M. Antosh, C. Chang, C. Schorl, S. Kolli, N. Neretti and S. L. Helfand (2010). Comparative transcriptional profiling identifies takeout as a gene that regulates life span. *Aging (Albany NY)*, 2(5): 298.

Bauer, J. H., P. C. Poon, H. Glatt-Deeley, J. M. Abrams and S. L Helfand (2005). Neuronal expression of p53 dominant-negative proteins in adult Drosophila melanogaster extends life span. *Current Biology*, 15(22): 2063–2068.

Benigni, A., D. Corna, C. Zoja, A. Sonzogni, R. Latini, M. Salio, S. Conti, D. Rottoli, L. Longaretti and P. Cassis (2009). Disruption of the Ang II type 1 receptor promotes longevity in mice. *The Journal of clinical investigation*, 119(3): 524–530.

Bernardes, de Jesus B., K. Schneeberger, E. Vera, A. Tejera, C. B. Harley and M. A. Blasco (2011). The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. *Aging cell*, 10(4): 604–621.

Bernardes, de Jesus B., E. Vera, K. Schneeberger, A. M. Tejera, E. Ayuso, F. Bosch and M. A. Blasco (2012). Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Molecular Medicine*, 4(8): 691–704.

Bhatia-Dey, N., R. R. Kanherkar, S. E. Stair, E. O. Makarev and A. B. Csoka (2016). Cellular senescence as the causal nexus of aging. *Frontiers in Genetics*, 7: 13.

Blackburn, E. H., E. S. Epel and J. Lin (2015). Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science*, 350(6265): 1193 – 1198.

Blackwell, T. K., M. J. Steinbaugh, J. M. Hourihan, C. Y. Ewald and M. Isik (2015). SKN-1/Nrf, stress responses, and aging in Caenorhabditis elegans. *Free Radical Biology and Medicine*, 88: 290–301.

Blasco, M. A., H. W. Lee, M. P. Hande, E. Samper, P. M. Lansdorp, R. A. DePinho and C. W. Greider (1997). Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. *Cell*, 91(1): 25–34.

Blüher, M., B. B. Kahn and C. R. Kahn (2003). Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science*, 299(5606): 572–574.

Boccardi, V. and U. Herbig (2012). Telomerase gene therapy: a novel approach to combat aging. *EMBO Molecular Medicine*, 4(8): 685–687.

Bodnar, A. G., M. Ouellette, M. Frolkis, S. E. Holt, C. P. Chiu, G. B. Morin, C. B. Harley, J. W. Shay, S. Lichtsteiner and W. E. Wright (1998). Extension of life-span by introduction of telomerase into normal human cells. *Science*, 279(5349): 349–352.

Broughton, S. J., M.D.W. Piper, T. Ikeya, T. M. Bass, J. Jacobson, Y. Driege, P. Martinez, E. Hafen, D. J. Withers and S. J. Leevers (2005). Longer lifespan, altered metabolism, and stress resistance in Drosophila from ablation of cells making insulin-like ligands. *Proceedings of the National Academy of Sciences*, 102(8): 3105–3110.

Brownborg, H. M., K. E. Borg, C. J. Meliska and A. Bartke (1996). Dwarf mice and the aging process. *Nature*, 384(6604): 33.

Canaan, A., J. DeFuria, E. Perelman, V. Schultz, M. Seay, D. Tuck, R. A. Flavell, M. P. Snyder, M. S. Obin and S. M. Weissman (2014). Extended lifespan and reduced adiposity in mice lacking the FAT10 gene. *Proceedings of the National Academy of Sciences*, 111(14): 5313–5318.

Canela, A., J. Martin-Caballero, J. M. Flores and M. A. Blasco (2004). Constitutive expression of tert in thymocytes leads to increased incidence and dissemination of T-cell lymphoma in Lck-Tert mice. *Molecular and cellular biology*, 24(10): 4275–4293.

Cao, L., X. Xu, S. F. Bunting, J. Liu, R. H. Wang, L. L. Cao, J. J. Wu, T. N. Peng, J. Chen and A. Nussenzweig (2009). A selective requirement for 53BP1 in the biological response to genomic instability induced by Brca1 deficiency. *Molecular cell*, 35(4): 534–541.

Chamberlain, J. R. and J. S. Chamberlain (2017). Progress toward Gene Therapy for Duchenne Muscular Dystrophy. *Molecular Therapy*, 25(5): 1125–1131.

Chavous, D. A., F. R. Jackson and C. M. O'Connor (2001). Extension of the Drosophila lifespan by overexpression of a protein repair methyltransferase. *Proceedings of the National Academy of Sciences*, 98(26): 14814–14818.

Chiu, C. H., W. D. Lin, S. Y. Huang and Y. H. Lee (2004). Effect of a C/EBP gene replacement on mitochondrial biogenesis in fat cells. *Genes & development*, 18(16): 1970–1975.

Choudhury, A. R., Z. Ju, M. W. Djojosubroto, A. Schienke, A. Lechel, S. Schaetzlein, H. Jiang, A. Stepczynska, C. Wang and J. Buer (2007). Cdkn1a deletion improves stem cell function and lifespan of mice with dysfunctional telomeres without accelerating cancer formation. *Nature genetics*, 39(1): 99–105.

Clancy, D. J., D. Gems, L. G. Harshman, S. Oldham, H. Stocker, E. Hafen, S. J. Leevers and L. Partridge (2001). Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein. *Science*, 292(5514): 104–106.

Conover, C. A. and L. K. Bale (2007). Loss of pregnancy-associated plasma protein A extends lifespan in mice. *Aging cell*, 6(5): 727–729.

Conti, B., M. Sanchez-Alavez, R. Winsky-Sommerer, M. C. Morale, J. Lucero, S. Brownell, V. Fabre, S. Huitron-Resendiz, S. Henriksen and E. P. Zorrilla (2006). Transgenic mice with a reduced core body temperature have an increased life span. *Science*, 314(5800): 825–828.

Copeland, J. M., J. Cho, T. Lo, J. H. Hur, S. Bahadorani, T. Arabyan, J. Rabie, J. Soh and D. W. Walker (2009). Extension of Drosophila life span by RNAi of the mitochondrial respiratory chain. *Current Biology*, 19(19): 1591–1598.

Coschigano, K. T., A. N. Holland, M. E. Riders, E. O. List, A. Flyvbjerg and J. J. Kopchick (2003). Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. *Endocrinology*, 144(9): 3799–3810.

Cutler, R. G. (2005). Oxidative stress and aging: catalase is a longevity determinant enzyme. *Rejuvenation research*, 8(3): 138–140.

Cvejic, S., Z. Zhu, S. J. Felice, Y. Berman and X. Y Huang. (2004). The endogenous ligand Stunted of the GPCR Methuselah extends lifespan in Drosophila. *Nature cell biology*, 6(6): 540–546.

Dell'agnello, C., S. Leo, A. Agostino, G. Szabadkai, C. Tiveron, A. Zulian, A. Prelle, P. Roubertoux, R. Rizzuto and M. Zeviani (2007). Increased longevity and refractoriness to Ca(2+)-dependent neurodegeneration in Surf1 knockout mice. *Human molecular genetics*, 16(4): 431–444.

Demontis, F. and N. Perrimon (2010). FOXO/4E-BP signaling in Drosophila muscles regulates organism-wide proteostasis during aging. *Cell*, 143(5): 813–825.

Demontis, F., V. K. Patel, W. R. Swindell and N. Perrimon (2014). Intertissue control of the nucleolus via a

myokine-dependent longevity pathway. *Cell reports*, 7(5): 1481–1494.
Doze, V. A., R. S. Papay, B. L. Goldenstein, M. K. Gupta, K. M. Collette, B. W. Nelson, M. J. Lyons, B. A. Davis, E. J. Luger and S. G. Wood (2011). Long-term α1A-adrenergic receptor stimulation improves synaptic plasticity, cognitive function, mood, and longevity. *Molecular pharmacology*, 80(4): 747–758.
Dunbar, C. E., K. A. High, J. K. Joung, D. B. Kohn, K. Ozawa and M. Sadelain (2018). Gene therapy comes of age. *Science*, 359(6372): eaan4672.
Ehmann, W. C., C. S. Rabkin, M. E. Eyster and J. J. Goedert (1997). Thrombocytopenia in HIV-infected and uninfected hemophiliacs. *American journal of hematology*, 54(4): 296–300.
Enns, L. C., J. F. Morton, P. R. Treuting, M. J. Emond, N. S. Wolf, D. F. Dai, G. S. McKnight, P. S. Rabinovitch and W. C. Ladiges (2009). Disruption of protein kinase A in mice enhances healthy aging. *PloS One*, 4(6): e5963.
Eren, M., A. E. Boe, S. B. Murphy, A. T. Place, V. Nagpal, L. Morales-Nebreda, D. Urich, S. E. Quaggin, G. R. S. Budinger and G. M. Mutlu (2014). PAI-1–regulated extracellular proteolysis governs senescence and survival in Klotho mice. *Proceedings of the National Academy of Sciences*, 111(19): 7090–7095.
Erwin, A. A. and J. P Blumenstiel (2019). Aging in the Drosophila ovary: contrasting changes in the expression of the piRNA machinery and mitochondria but no global release of transposable elements. *BMC genomics*, 20(1): 305.
Fedarko, N. S (2018). Theories and mechanisms of aging. *Geriatric Anesthesiology*. Springer, pp. 19–25.
Flatt, T., K. J. Min, C. D'Alterio, E. Villa-Cuesta, J. Cumbers, R. Lehmann, D. L. Jones and M. Tatar (2008). Drosophila germ-line modulation of insulin signaling and lifespan. *Proceedings of the National Academy of Sciences*, 105(17): 6368–6373.
Flores, I., M. L. Cayuela and M. A Blasco (2005). Effects of telomerase and telomere length on epidermal stem cell behavior. *Science*, 309(5738): 1253–1256.
Flores, I., A. Canela, E. Vera, A. Tejera, G. Cotsarelis and M. A Blasco (2008). The longest telomeres: a general signature of adult stem cell compartments. *Genes & development*, 22(5): 654–667.
Flurkey, K., J. Papaconstantinou, R. A. Miller and D. E. Harrison (2001). Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proceedings of the National Academy of Sciences*, 98(12): 6736–6741.
Fossel, M. (1998). Telomerase and the aging cell: implications for human health. *JAMA*, 279(21): 1732–1735.
Fridell, Y. W. C., A. Sánchez-Blanco, B. A. Silvia and S. L. Helfand (2005). Targeted expression of the human uncoupling protein 2 (hUCP2) to adult neurons extends life span in the fly. *Cell metabolism*, 1(2): 145–152.
Funk, W. D., C. K. Wang, D. N. Shelton, C. B. Harley, G. D. Pagon and W. K. Hoeffler (2000). Telomerase expression restores dermal integrity to in vitro-aged fibroblasts in a reconstituted skin model. *Experimental cell research*, 258(2): 270–278.
Garcia-Cao, I., M. Garcia-Cao, A. Tomas-Loba, J. Martin-Caballero, J. M. Flores, P. Klatt, M. A. Blasco and M. Serrano (2006). Increased p53 activity does not accelerate telomere-driven ageing. *EMBO reports*, 7(5): 546–552.
Gassen, N. C., G. P. Chrousos, E. B. Binder and A. S. Zannas (2017). Life stress, glucocorticoid signaling, and the aging epigenome: Implications for aging-related diseases. *Neuroscience & Biobehavioral Reviews*, 74: 356–365.
Gimenez, L. E. D., P. K. E. Ghildyal, H. Fischer, Hu, W.W. Ja, B. A. Eaton, Y. Wu, S. N. Austad and R. Ranjan (2013). Modulation of methuselah expression targeted to Drosophila insulin-producing cells extends life and enhances oxidative stress resistance. *Aging cell*, 12(1): 121–129.
Giorgi, C., S. Marchi, I. C. M. Simoes, Z. Ren, G. Morciano, M. Perrone, P. Patalas-Krawczyk, S. Borchard, P. Jędrak, K. Pierzynowska, J. Szymański, D. Q. Wang, P. Portincasa, G. Węgrzyn, H. Zischka, P. Dobrzyn, M. Bonora, J. Duszynski, A. Rimessi, A. Karkucinska-Wieckowska, A. Dobrzyn, G. Szabadkai, B. Zavan, P.J. Oliveira, V.A. Sardao, P. Pinton and M.R. Wieckowski (2018). Mitochondria and Reactive Oxygen Species in Aging and Age-Related Diseases. *Int Rev Cell Mol Biol*., 340: 209-344. doi: 10.1016/bs.ircmb.2018.05.006.
Gonzalez-Suarez, E., E. Samper, A. Ramirez, J. M. Flores, J. Martin-Caballero, J. L. Jorcano and M. A. Blasco (2001). Increased epidermal tumors and increased skin wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes. *The EMBO journal*, 20(11): 2619–2630.
Gorbunova, V. and A. Seluanov (2016). DNA double strand break repair, aging and the chromatin connection. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 788: 2–6.
Hakimi, P., J. Yang, G. Casadesus, D. Massillon, F. Tolentino-Silva, C. K. Nye, Cabrera, M. E. Hagen, D. R. Utter, C. B. and Y. Baghdy (2007). Overexpression of the cytosolic form of phosphoenolpyruvate carboxykinase (GTP) in skeletal muscle repatterns energy metabolism in the mouse. *Journal of Biological Chemistry*, 282(45):

32844–32855.
Hanna, E., C. Rémuzat, P. Auquier and M. Toumi (2017). Gene therapies development: slow progress and promising prospect. *Journal of Market Access & Health Policy*, 5(1): 1265293.
Harper, J. M., J. E. Wilkinson and R. A. Miller (2010). Macrophage migration inhibitory factor-knockout mice are long lived and respond to caloric restriction. *The FASEB Journal*, 24(7): 2436–2442.
Hart, S. L. and P. T. Harrison (2017). Genetic therapies for cystic fibrosis lung disease. *Current Opinion in Pharmacology*, 34: 119–124.
Helfand, S. L., J. Wood, B. C. Jones and J. Taylor (2017). Activation Of Transposable Elements As A Molecular Cause Of Aging. *Innovation in Aging*, 1(suppl_1): 1333.
Herrera, E., E. Samper, J. Martín-Caballero, J. M. Flores, H. Lee and M. A. Blasco (1999). Disease states associated with telomerase deficiency appear earlier in mice with short telomeres. *The EMBO Journal*, 18(11): 2950–2960.
Hofmann, J. W., X. Zhao, M. De Cecco, A. L. Peterson, L. Pagliaroli, J. Manivannan, G. B. Hubbard, Y. Ikeno, Y. Zhang and B. Feng (2015). Reduced expression of MYC increases longevity and enhances healthspan. *Cell*, 160(3): 477–488.
Holzenberger, M., J. Dupont, B. Ducos, P. Leneuve, A. Géloën, P. C. Even, P. Cervera and Y. Le Bouc (2003). IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature*, 421(6919): 182–187.
Hwangbo, D. S., B. Gersham, M. P. Tu, M. Palmer and M. Tatar, (2004). Drosophila dFOXO controls lifespan and regulates insulin signalling in brain and fat body. *Nature*, 429(6991): 562–566.
Inoue, T., M. Ailion, S. Poon, H. K. Kim, J. H. Thomas and P. W. Sternberg (2007). Genetic analysis of dauer formation in Caenorhabditis briggsae. *Genetics*, 177(2): 809–818.
Jäger, K. and M. Walter (2016). Therapeutic Targeting of Telomerase. *Genes* , 7(7): 39.
Janac, S., B. Clarke, and D. Gems (2017). Aging: Natural or disease? A view from medical textbooks. *Anti-aging drugs: from basic research to clinical practice. R. Soc. Chem*, : 11–34.
Jaskelioff, M., F. L. Muller, J. H. Paik, E. Thomas, S. Jiang, A. C. Adams, E. Sahin, M. Kost-Alimova, A. Protopopov, J. Cadinanos, J. W. Horner, E. Maratos-Flier and R. A. Depinho (2011). Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature*, 469(7328): 102–106.
Johnson, T. E (1990). Increased life-span of age-1 mutants in Caenorhabditis elegans and lower Gompertz rate of aging. *Science*, 249(4971): 908–912.
Kabil, H., O. Kabil, R. Banerjee, L. G. Harshman and S. D. Pletcher (2011). Increased transsulfuration mediates longevity and dietary restriction in Drosophila. *Proceedings of the National Academy of Sciences*, 108(40): 16831–16836.
Kapahi, P., B. M. Zid, T. Harper, D. Koslover, V. Sapin and S. Benzer (2004). Regulation of lifespan in Drosophila by modulation of genes in the TOR signaling pathway. *Current Biology*, 14(10): 885–890.
Kappeler, L., C. De Magalhaes Filho, J. Dupont, P. Leneuve, P. Cervera, L. Périn, C. Loudes, A. Blaise, R. Klein and J. Epelbaum (2008). Brain IGF-1 receptors control mammalian growth and lifespan through a neuroendocrine mechanism. *PLoS Biology*, 6(10): e254.
Katayama, M., T. Kiyono, K. Horie, T. Hirayama, T. Eitsuka, K. Kuroda, K. Donai, S. Hidema, K. Nishimori and T. Fukuda (2015). Establishment of an immortalized cell line derived from the prairie vole via lentivirus-mediated transduction of mutant cyclin-dependent kinase 4, cyclin D, and telomerase reverse transcriptase. *Experimental Animals*, 15-0061.
Kauppila, T. E. S., J. H. K. Kauppila and N. G. Larsson (2017). Mammalian mitochondria and aging: an update. *Cell metabolism*, 25(1): 57–71.
Keller, M. D., L. D. Notarangelo and H. L Malech (2018). Future of Care for Patients With Chronic Granulomatous Disease: Gene Therapy and Targeted Molecular Medicine. *Journal of the Pediatric Infectious Diseases Society*, 7(suppl_1): S40–S44.
Kim, G. H., Y. E. Lee, G. H. Lee, Y. H. Cho, Y. N. Lee, Y. Jang, D. Paik and J. J. Park (2015). Overexpression of malic enzyme in the larval stage extends Drosophila lifespan. *Biochemical and biophysical research communications*, 456(2): 676–682.
Kohn, D. B (2019). Gene therapy for blood diseases. *Current Opinion in Biotechnology*, 60: 39–45.
Landis, G. N., D. Bhole and J. Tower (2003). A search for doxycycline-dependent mutations that increase Drosophila melanogaster life span identifies the VhaSFD, Sugar baby, filamin, fwd and Cctl genes. *Genome Biology*, 4(2): R8.
Larrick, J. W. and A. R. Mendelsohn (2015). Telomerase Redux: Ready for Prime Time? *Rejuvenation Research*, 18(2): 185–187.
Larsen, P. D. (2019). Geroscience: The Intersection of Basic Aging Biology, Chronic Disease, and Health, 187-188.
Lasry, A., and Y. Ben-Neriah (2015). Senescence-associated inflammatory responses: aging and cancer

perspectives. *Trends in Immunology*, 36(4): 217–228.

Lee, K. S., K. Iijima-Ando, K. Iijima, W. J. Lee, J. H. Lee, K. Yu and D. S. Lee (2009). JNK/FOXO-mediated neuronal expression of fly homologue of peroxiredoxin II reduces oxidative stress and extends life span. *Journal of Biological Chemistry*, 284(43): 29454–29461.

Lee, S. H., S. K. Lee, D. Paik and K. J. Min (2012). Overexpression of Fatty-Acid-***β***-Oxidation-Related Genes Extends the Lifespan of Drosophila melanogaster. *Oxidative medicine and cellular longevity*.

Legan, S. K., I. Rebrin, R. J. Mockett, S. N. Radyuk, V. I. Klichko, R. S. Sohal and W. C. Orr (2008). Overexpression of glucose-6-phosphate dehydrogenase extends the life span of Drosophila melanogaster. *Journal of Biological Chemistry*, 283(47): 32492–32499.

Li, W., L. Prazak, N. Chatterjee, S. Grüninger, L. Krug, D. Theodorou and J. Dubnau (2013). Activation of transposable elements during aging and neuronal decline in Drosophila. *Nature Neuroscience*, 16(5): 529–531.

Li, Y. and J. Tower (2009). Adult-specific over-expression of the Drosophila genes magu and hebe increases life span and modulates late-age female fecundity. *Molecular Genetics and Genomics*, 281(2): 147–162.

Lin, M. J., L. Y. Tang, M. N. Reddy and C. K. J. Shen (2005). DNA methyltransferase gene dDnmt2 and longevity of Drosophila. *Journal of Biological Chemistry*, 280(2): 861–864.

Lin, R., A. Angelin, F. Da Settimo, C. Martini, S. Taliani, S. Zhu and D. C. Wallace (2014). Genetic analysis of dTSPO, an outer mitochondrial membrane protein, reveals its functions in apoptosis, longevity, and Aβ42-induced neurodegeneration. *Aging cell*, 13(3): 507–518.

Lin, Y., Y. Chen, T. Kao, Y. Lin, T. Hsu, Y. Wu, W. W. Ja, T. J. Brummel, P. Kapahi and C. Yuh (2014). Diacylglycerol lipase regulates lifespan and oxidative stress response by inversely modulating TOR signaling in Drosophila and C. elegans. *Aging cell*, 13(4): 755–764.

Liu, J., L. Wang, Z. Wang and J. P. Liu, (2019). Roles of Telomere Biology in Cell Senescence, Replicative and Chronological Ageing. *Cells*, 8(1): 54.

Liu, X., N. Jiang, B. Hughes, E. Bigras, E. Shoubridge and S. Hekimi (2005). Evolutionary conservation of the clk-1-dependent mechanism of longevity: loss of mclk1 increases cellular fitness and lifespan in mice. *Genes & development*, 19(20): 2424–2434.

Liu, Y., W. Lu, T. J. Brummel, C. Yuh, P. Lin, T. Kao, F. Li, P. Liao, S. Benzer and H. Wang (2009). Reduced expression of alpha-1, 2-mannosidase I extends lifespan in Drosophila melanogaster and Caenorhabditis elegans. *Aging cell*, 8(4): 370–379.

Loboda, A., M. Damulewicz, E. Pyza, A. Jozkowicz and J. Dulak (2016). Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. *Cellular and Molecular Life Sciences*, 73(17): 3221–3247.

López-Andrés, N., L. Calvier, C. Labat, R. Fay, J. Díez, A. Benetos, F. Zannad, P. Lacolley and P. Rossignol (2013). Absence of cardiotrophin 1 is associated with decreased age-dependent arterial stiffness and increased longevity in mice. *Hypertension*, 61(1): 120–129.

Loreto, E. L. S. and C. M. Pereira (2017). Somatizing the transposons action. *Mobile genetic elements*, 7(3): 1–9.

Luca, G., I. Ventura, V. Sanghez, M. T. Russo, M. A. Ajmone-Cat., E. Cacci, A. Martire, P. Popoli, G. Falcone and F. Michelini (2013). Prolonged lifespan with enhanced exploratory behavior in mice overexpressing the oxidized nucleoside triphosphatase hMTH1. *Aging cell*, 12(4): 695–705.

Lundstrom, K. (2018). Viral Vectors in Gene Therapy. *Diseases* , 6(2):42.

Magwire, M. M., A. M. A.Yamamoto, N. V. Carbone, A. V. Roshina, Symonenko, E. G. Pasyukova, T. V . Morozova and T. F. C. Mackay (2010). Quantitative and molecular genetic analyses of mutations increasing Drosophila life span. *PLoS Genetics*, 6(7): e1001037.

Markovich, D., M. C. Ku and D. Muslim (2011). Increased lifespan in hyposulfatemic NaS1 null mice. *Experimental gerontology*, 46(10): 833–835.

McKay, J. D., R. J. Hung, V. Gaborieau, P. Boffetta, A. Chabrier, G. Byrnes, D. Zaridze, A. Mukeria, N. Szeszenia-Dabrowska, J. Lissowska, P. Rudnai, E. Fabianova, D. Mates, V. Bencko, L. Foretova, V. Janout, J. McLaughlin, F. Shepherd, A. Montpetit, *et al* (2008). Lung cancer susceptibility locus at 5p15.33. *Nature Genetics*, 40(12): 1404–1406.

Merino, M. M., C. Rhiner, J. M. Lopez-Gay, D. Buechel, B. Hauert and E. Moreno (2015). Elimination of unfit cells maintains tissue health and prolongs lifespan. *Cell*, 160(3): 461–476.

Migliaccio, E., M. Giorgio, S. Mele, G. Pelicci, P. Reboldi, P. P. Pandolfi, L. Lanfrancone and P. G. Pelicci (1999). The p66shc adaptor protein controls oxidative stress response and life span in mammals. *Nature*, 402(6759): 309–313.

Milholland, B., Y. Suh and J. Vijg (2017). Mutation and catastrophe in the aging genome. *Experimental Gerontology*, 94: 34–40.

Mistry, P. K., G. Lopez, R. Schiffmann, N. W. Barton, N. J. Weinreb and E. Sidransky (2017). Gaucher disease: Progress and ongoing challenges. *Molecular Genetics and Metabolism*, 120(1): 8–21.

Mitchell, J. R., E. Wood and K. Collins (1999). A telomerase component is defective in the human disease dyskeratosis congenita. *Nature*, 402(6761): 551–555.

Mitsui, A., J. H. Hamuro, Nakamura, Kondo, N. Hirabayashi, Y. Ishizaki-Koizumi, S. Hirakawa, T. Inoue and J. Yodoi (2002). Overexpression of human thioredoxin in transgenic mice controls oxidative stress and life span. *Antioxidants and Redox Signaling*, 4(4): 693–696.

Mockett, R. J., R. S. Sohal and W. C. Orr (1999). Overexpression of glutathione reductase extends survival in transgenic Drosophila melanogaster under hyperoxia but not normoxia. *The FASEB Journal*, 13(13): 1733–1742.

Morin, G. B (1989). The human telomere terminal transferase enzyme is a ribonucleoprotein that synthesizes TTAGGG repeats. *Cell*, 59(3): 521–529.

Mueller, C., G. Gernoux, A. M. Gruntman, F. Borel, E. P. Reeves, R. Calcedo, F. N Rouhani., A. Yachnis, M. Humphries, M. Campbell-Thompson, L. Messina, J. D. Chulay, B. Trapnell, J. M. Wilson, N. G. McElvaney and T. R. Flotte (2017). 5 Year Expression and Neutrophil Defect Repair after Gene Therapy in Alpha-1 Antitrypsin Deficiency. *Molecular Therapy*, 25(6): 1387–1394.

Muñoz-Lorente, M. A., A. C. Cano-Martin and M. A. Blasco (2019). Mice with hyper-long telomeres show less metabolic aging and longer lifespans. *Nature Communications*, 10(1): 4723.

Nielsen, M. D., X. Luo, B. Biteau, K. Syverson and H. Jasper (2008). 14-3-3ε antagonizes FoxO to control growth, apoptosis and longevity in Drosophila. *Aging cell*, 7(5): 688–699.

Nishimura, M., C. Kumsta, G. Kaushik, S. B. Diop, Y. Ding, J. Bisharat-Kernizan, H. Catan, A. Cammarato, R. S. Ross and A. J. Engler (2014). A dual role for integrin-linked kinase and β1-integrin in modulating cardiac aging. *Aging cell*, 13(3): 431–440.

Nissanka, N. and C. T. Moraes (2018). Mitochondrial DNA damage and reactive oxygen species in neurodegenerative disease. *FEBS Letters*, 592(5): 728–742.

Nojima, A., M. Yamashita, Y. Yoshida, I. Shimizu, H. Ichimiya, N. Kamimura, Y. Kobayashi, S. Ohta, N. Ishii and T. Minamino (2013). Haploinsufficiency of akt1 prolongs the lifespan of mice. *PloS one*, 8(7): e69178.

Oklejewicz, M. and S. Daan (2002). Enhanced longevity in tau mutant Syrian hamsters, Mesocricetus auratus. *Journal of biological rhythms*, 17(3): 210–216.

Orr, W. C. and R. S.Sohal (1994). Extension of life-span by overexpression of superoxide dismutase and catalase in Drosophila melanogaster. *Science*, 263(5150): 1128–1130.

Orr, W. C., S. N. Radyuk, L. Prabhudesai, D. Toroser, J. J. Benes, J. M. Luchak, R. J. Mockett, I. Rebrin, J. G. Hubbard and R. S. Sohal (2005). Overexpression of glutamate-cysteine ligase extends life span in Drosophila melanogaster. *Journal of Biological Chemistry*, 280(45): 37331–37338.

Orr, W. C (2016). Tightening the connection between transposable element mobilization and aging. *Proceedings of the National Academy of Sciences*, 113(40): 11069–11070.

Owusu-Ansah, E., W. Song and N. Perrimon (2013). Muscle mitohormesis promotes longevity via systemic repression of insulin signaling. *Cell*, 155(3): 699–712.

Ozturk, B. M., Y. Li and V. Tergaonkar (2017). Current Insights to Regulation and Role of Telomerase in Human Diseases. *Antioxidants*, 6(1): 17.

Pan, M. R., K. Li, S. Y. Lin and W. C. Hung (2016). Connecting the dots: from DNA damage and repair to aging. *International journal of molecular sciences*, 17(5): 685.

Panich, U., G. Sittithumcharee, N. Rathviboon and S. Jirawatnotai (2016). Ultraviolet radiation-induced skin aging: the role of DNA damage and oxidative stress in epidermal stem cell damage mediated skin aging. *Stem cells international*, 2016:7370642. doi: 10.1155/2016/7370642.

Panowski, S. H., S. Wolff, H. Aguilaniu, J. Durieux and A. Dillin (2007). PHA-4/Foxa mediates diet-restriction-induced longevity of C. elegans. *Nature*, 447(7144): 550–555.

Perez, G. I., A. Jurisicova, L. Wise, T. Lipina, M. Kanisek, A. Bechard, Y. Takai, P. Hunt, J. Roder and M. Grynpas (2007). Absence of the proapoptotic Bax protein extends fertility and alleviates age-related health complications

in female mice. *Proceedings of the National Academy of Sciences*, 104(12): 5229–5234.
Piano, A. and V. I Titorenko (2015). The intricate interplay between mechanisms underlying aging and cancer. *Aging and disease*, 6(1): 56.
Pinto, M. and C. T. Moraes, (2015). Mechanisms linking mtDNA damage and aging. *Free radical biology & medicine*, 85: 250–258.
Plyusnina, E. N., M. V. Shaposhnikov and A. A. Moskalev (2011). Increase of Drosophila melanogaster lifespan due to D-GADD45 overexpression in the nervous system. *Biogerontology*, 12(3): 211–226.
Poon, P. C., T. H. Kuo, N. J. Linford, G. Roman and S. D. Pletcher (2010). Carbon dioxide sensing modulates lifespan and physiology in Drosophila. *PLoS Biology*, 8(4): e1000356.
Proshkina, E. N., M. V. Shaposhnikov, A. F. Sadritdinova, A.V. Kudryavtseva and A. A. Moskalev (2015). Basic mechanisms of longevity: A case study of Drosophila pro-longevity genes. *Ageing Research Reviews*, 24: 218–231.
Pyo, J. O., S. M. Yoo, H. H. Ahn, J. Nah, S. H. Hong, T. I. Kam, S. Jung and Y. K Jung (2013). Overexpression of Atg5 in mice activates autophagy and extends lifespan. *Nature communications*, 4(1): 1-9.
Radman, M. (2016). Protein damage, radiation sensitivity and aging. *DNA Repair*, 44: 186–192.
Radyuk, S. N., K. Michalak, V. I. Klichko, J. Benes, I. Rebrin, R. S. Sohal and W. C. Orr (2009). Peroxiredoxin 5 confers protection against oxidative stress and apoptosis and also promotes longevity in Drosophila. *Biochemical Journal*, 419(2): 437–445.
Rafna,r T., P. Sulem, S. N. Stacey, F. Geller, J. Gudmundsson, A. Sigurdsson, M. Jakobsdottir, H. Helgadottir, S. Thorlacius, K. K. Aben, T. Blondal, T. E.Thorgeirsson, G. Thorleifsson, K. Kristjansson, K. Thorisdottir, R. Ragnarsson, B. Sigurgeirsson, H. Skuladottir, T. Gudbjartsson, *et al.* (2009). Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. *Nature Genetics*, 41(2): 221–227.
Ramunas, J., E. Yakubov, J. J. Brady, S. Y. Corbel, C. Holbrook, M. Brandt, J. Stein, J. G. Santiago, J. P. Cooke and H. M. Blau (2015). Transient delivery of modified mRNA encoding TERT rapidly extends telomeres in human cells. *The FASEB Journal*, 29(5): 1930–1939.
Ran, Q., H. Liang, Y. Ikeno, W. Qi, T. A. Prolla, L. J. Roberts, N. Wolf, H. VanRemmen and A. Richardson (2007). Reduction in glutathione peroxidase 4 increases life span through increased sensitivity to apoptosis. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 62(9): 932–942.
Rana, A., M. Rera and D. W. Walker (2013). Parkin overexpression during aging reduces proteotoxicity, alters mitochondrial dynamics, and extends lifespan. *Proceedings of the National Academy of Sciences*, 110(21): 8638–8643.
Rattan S. I. (2007). The science of healthy aging: genes, milieu, and chance. *Annals of the New York Academy of Sciences*, 1114(1): 1–10
Rattan, S. I. and R. Singh (2009). Progress & prospects: gene therapy in aging. *Gene Ther*., 16(1): 3–9.
Rera, M., S. Bahadorani, J. Cho, C. L. Koehler, M. Ulgherait, J. H. Hur, W. S. Ansari, T. Lo, D. L. Jones and D. W. Walker (2011). Modulation of longevity and tissue homeostasis by the Drosophila PGC-1 homolog. *Cell metabolism*, 14(5): 623–634.
Riera, C. E., M. O. Huising, P. Follett, M. Leblanc, J. Halloran, R. Van Andel C. D. de Magalhaes Filho, C. Merkwirth, and A. Dillin (2014). TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. *Cell*, 157(5): 1023–1036.
Rogina, B., S. L Helfand and S. Frankel (2002). Longevity regulation by Drosophila Rpd3 deacetylase and caloric restriction. *Science*, 298(5599): 1745.
Rotondo, D. and J. Davidson (2017). Gene therapy, a promising treatment for familial hypercholesterolaemia. *Current Opinion in Lipidology*, 28(2).
Ruan, H., X. D. Tang, M. L. Chen, M. A. Joiner, G. Sun, N. Brot, H. Weissbach, S. H. Heinemann, L. Iverson and C. F. Wu (2002). High-quality life extension by the enzyme peptide methionine sulfoxide reductase. *Proceedings of the National Academy of Sciences*, 99(5): 2748–2753.
Runko, A. P., A. J. Griswold and K. T. Min (2008). Overexpression of frataxin in the mitochondria increases resistance to oxidative stress and extends lifespan in Drosophila. *FEBS letters*, 582(5): 715–719.
Sánchez-Blanco, A., Y. W. C. Fridell and S. L. Helfand (2006). Involvement of Drosophila uncoupling protein 5 in metabolism and aging. *Genetics*, 172(3): 1699–1710.
Schoeftner, S., R. Blanco, I. Lopez de Silanes, P. Munoz, G. J. M. Gomez-Lopez, Flores and M. A. Blasco (2009). Telomere shortening relaxes X chromosome inactivation and forces global transcriptome alterations. *Proceedings of the National Academy of Sciences*, 106(46): 19393–19398.
Schriner, S. E., N. J. Linford, G. M. Martin, P. Treuting, C. E. Ogburn, M. Emond, P. E. Coskun, W. Ladiges, N. Wolf and H. Van Remmen (2005). Extension of murine life span by overexpression of catalase targeted to

mitochondria. *Science*, 308(5730): 1909–1911.
Schriner, S. E. and N. J. Linford (2006). Extension of mouse lifespan by overexpression of catalase. *Age*, 28(2): 209–218.
Selman, C., S. Lingard, A. I. Choudhury, R. L. Batterham, M. Claret, M. Clements, F. Ramadani, K. Okkenhaug, E. Schuster and E. Blanc (2008). Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice. *The FASEB Journal*, 22(3): 807–818.
Selman, C., J. M. A. Tullet, D. Wieser, E. Irvine, S. J. Lingard, A. I. Choudhury, M. Claret, H. Al-Qassab, D. Carmignac and F. Ramadani (2009). Ribosomal protein S6 kinase 1 signaling regulates mammalian life span. *Science*, 326(5949): 140–144.
Seong, K. H., T. Matsuo, Y. Fuyama and T. Aigaki (2001). Neural-specific overexpression of Drosophila Plenty of SH3s (DPOSH) extends the longevity of adult flies. *Biogerontology*, 2(4): 271–281.
Sgro, C. M. and L. Partridge, (1999). A delayed wave of death from reproduction in Drosophila. *Science*, 286(5449): 2521–2524.
Shepherd, J. C., U. Walldorf, P. Hug and W. J. Gehring (1989). Fruit flies with additional expression of the elongation factor EF-1 alpha live longer. *Proceedings of the National Academy of Sciences*, 86(19): 7520–7521.
Sidler, C., O. Kovalchuk and I. Kovalchuk (2017). Epigenetic Regulation of Cellular Senescence and Aging. *Frontiers in Genetics*, 8: 138.
Siebold, A. P., R. Banerjee, F. Tie, D. L. Kiss, J. Moskowitz and P. J. Harte (2010). Polycomb Repressive Complex 2 and Trithorax modulate Drosophila longevity and stress resistance. *Proceedings of the National Academy of Sciences*, 107(1): 169–174.
Simon, A. F., C. Shih, A. Mack and S. Benzer (2003). Steroid control of longevity in Drosophila melanogaster. *Science*, 299(5611): 1407–1410.
Simons, M. J. P. (2015). Questioning causal involvement of telomeres in aging. *Ageing Research Reviews*, 24: 191–196.
Simonsen, A., R. C. Cumming, K. Lindmo, V. Galaviz, S. Cheng, T. E. Rusten and K. D. Finley (2007). Genetic modifiers of the Drosophila blue cheese gene link defects in lysosomal transport with decreased life span and altered ubiquitinated-protein profiles. *Genetics*, 176(2): 1283–1297.
Simonsen, A., R. C. Cumming, A. Brech, P. Isakson, D. R. Schubert and K. D. Finley (2008). Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult Drosophila. *Autophagy*, 4(2): 176–184.
Sinadinos, C., J. Valles-Ortega, L. Boulan, E. Solsona, M. F. Tevy, M. Marquez, J. Duran, C. Lopez-Iglesias, J. Calbó and E. Blasco (2014). Neuronal glycogen synthesis contributes to physiological aging. *Aging cell*, 13(5): 935–945.
Singh S. P., M. Niemczyk, D. Saini, V. Sadovov, L. Zimniak and P. Zimniak (2010). Disruption of the mGsta4 gene increases life span of C57BL mice. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 65(1): 14–23
Smith, M. C., E. T. Goddard, M. Perusina Lanfranca and D. J. Davido (2013). hTERT Extends the Life of Human Fibroblasts without Compromising Type I Interferon Signaling. *PloS one*, 8(3): e58233.
Song, W., D. Ren, W. Li, L. Jiang, K. W. Cho, P. Huang, C. Fan, Y. Song, Y. Liu and L. Rui (2010). SH2B regulation of growth, metabolism, and longevity in both insects and mammals. *Cell metabolism*, 11(5): 427–437
Srivastava, S. (2017). The mitochondrial basis of aging and age-related disorders. *Genes*, 8(12): 398.
Streeper, R. S., C. A. Grueter, N. Salomonis, S. Cases, M. C. Levin, S. K. Koliwad, P. Zhou, M. D. Hirschey, E. Verdin and R.V. Farese Jr (2012). Deficiency of the lipid synthesis enzyme, DGAT1, extends longevity in mice. *Aging (Albany NY)*, 4(1): 13–27.
Sturm, A., Z. Ivics and T. Vellai (2015). The mechanism of ageing: primary role of transposable elements in genome disintegration. *Cellular and molecular life sciences*, 72(10): 1839–1847.
Suh, J. M., D. Stenesen, J. M. Peters, A. Inoue, A. Cade and J. M. Graff (2008). An RGS-containing sorting nexin controls Drosophila lifespan. *PloS one*, 3(5): e2152.
Sun, L. Y., A. Spong, W. R. Swindell, Y. Fang, C. Hill, J. A. Huber, J. D. Boehm, R. Westbrook, R. Salvatori and A. Bartke (2013). Growth hormone-releasing hormone disruption extends lifespan and regulates response to caloric restriction in mice. e*life*, 2: e01098.
Sykiotis, G. P. and D. Bohmann (2008). Keap1/Nrf2 signaling regulates oxidative stress tolerance and lifespan in Drosophila. *Developmental cell*, 14(1): 76–85.
Tacutu, R., D. Thornton, E. Johnson, A. Budovsky, D. Barardo, T. Craig, E. Diana, G. Lehmann, D. Toren, J. Wang, V. E. Fraifeld and J. P. de Magalhães (2018). Human Ageing Genomic Resources: new and updated databases. *Nucleic acids research*, 46(D1): D1083–D1090.

Taguchi, A., L. M. Wartschow and M. F. White (2007). Brain IRS2 signaling coordinates life span and nutrient homeostasis. *Science*, 317(5836): 369–372.

Takahashi, K., Y. Noda., I. Ohsawa, T. Shirasawa and M. Takahashi (2014). Extended lifespan, reduced body size and leg skeletal muscle mass, and decreased mitochondrial function in clk-1 transgenic mice. *Experimental gerontology*, 58: 146–153.

Tatar, M., A. A. Khazaeli and J. W. Curtsinger (1997). Chaperoning extended life. *Nature*, 390(6655): 30.

Tatar, M., A. Kopelman, D. Epstein, M. P. Tu, C. M. Yin and R. S. Garofalo (2001). A mutant Drosophila insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science*, 292(5514): 107–110.

Tatar, M., A. Bartke and A. Antebi (2003). The endocrine regulation of aging by insulin-like signals. *Science*, 299(5611): 1346–1351.

Theurey, P. and P. Pizzo (2018). The aging mitochondria. *Genes*, 9(1): 22.

Tocchetti, A., C. B. E. Soppo, F. Zani, F. Bianchi, M. C. Gagliani, B. Pozzi, J. Rozman, R. Elvert, N. Ehrhardt and B. Rathkolb (2010). Loss of the actin remodeler Eps8 causes intestinal defects and improved metabolic status in mice. *PloS one*, 5(3): e9468.

Todd, A. M. and B. E. Staveley (2012). Expression of Pink1 with alpha-synuclein in the dopaminergic neurons of Drosophila leads to increases in both lifespan and healthspan. *Genetics and Molecular Research*, 11(2): 1497–1502.

Tomas-Loba, A., I. Flores, P. J. Fernandez-Marcos, M. L. Cayuela, A. Maraver, A. Tejera, C. Borras, A. Matheu, P. Klatt, J. M. Flores, J. Vina, M. Serrano and M. A. Blasco (2008). Telomerase reverse transcriptase delays aging in cancer-resistant mice. *Cell*, 135(4): 609–622.

Tong, J. J., S. E. Schriner, D. McCleary, B. J. Day and D. C. Wallace (2007). Life extension through neurofibromin mitochondrial regulation and antioxidant therapy for neurofibromatosis-1 in Drosophila melanogaster. *Nature genetics*, 39(4): 476–485.

Tsakiri, K. D., J. T. Cronkhite, P. J. Kuan, C. Xing, G. Raghu, J. C. Weissler, R. L. Rosenblatt, J. W. Shay and C. K. Garcia (2007). Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proceedings of the National Academy of Sciences*, 104(18): 7552–7557.

Tucker, K., J. M. Overton and D. A. Fadool (2008). Kv1. 3 gene-targeted deletion alters longevity and reduces adiposity by increasing locomotion and metabolism in melanocortin-4 receptor-null mice. *International journal of obesity*, 32(8): 1222–1232.

Ulgherait, M., A. Rana, M. Rera, J. Graniel and D. W. Walker (2014). AMPK modulates tissue and organismal aging in a non-cell-autonomous manner. *Cell reports*, 8(6): 1767–1780.

Umeda-Kameyama, Y., M. Tsuda, C. Ohkura, T. Matsuo, Y. Namba, Y. Ohuchi and T. Aigaki (2007). Thioredoxin suppresses Parkin-associated endothelin receptor-like receptor-induced neurotoxicity and extends longevity in Drosophila. *Journal of Biological Chemistry*, 282(15): 11180–11187.

Vaziri, H. and S. Benchimol (1998). Reconstitution of telomerase activity in normal human cells leads to elongation of telomeres and extended replicative life span. *Current Biology*, 8(5): 279–282.

Vulliamy, T., A. Marrone, F. Goldman, A. Dearlove, M. Bessler, P. J. Mason and I. Dokal (2001). The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. *Nature*, 413(6854): 432–435.

Wang, C., Y. Chen, Y. Wang, M. Huang, T. Yen, H. Li, C. Liang, T. Sang, S. Ciou and C. Yuh (2012). Reduced neuronal expression of ribose-5-phosphate isomerase enhances tolerance to oxidative stress, extends lifespan, and attenuates polyglutamine toxicity in Drosophila. *Aging cell*, 11(1): 93–103.

Wang, D., Y. Cui, Z. Jiang and W. Xie (2014). Knockdown expression of eukaryotic initiation factor 5 C-terminal domain containing protein extends lifespan in Drosophila melanogaster. *Biochemical and biophysical research communications*, 446(2): 465–469.

Wang, H. D., P. Kazemi-Esfarjani and S. Benzer (2004). Multiple-stress analysis for isolation of Drosophila longevity genes. *Proceedings of the National Academy of Sciences*, 101(34): 12610–12615.

Wang, M. C., D. Bohmann and H. Jasper (2003). JNK signaling confers tolerance to oxidative stress and extends lifespan in Drosophila. *Developmental cell*, 5(5): 811–816.

Wang, X., K. Chrysovergis, J. Kosak, G. Kissling, M. Streicker, G. Moser, R. Li and T. E. Eling (2014). hNAG-1 increases lifespan by regulating energy metabolism and insulin/IGF-1/mTOR signaling. *Aging (Albany NY)*, 6(6).

Waterson, M. J., B. Y. Chung, Z. M. Harvanek, I. Ostojic, J. Alcedo and S. D. Pletcher (2014). Water sensor ppk28 modulates Drosophila lifespan and physiology through AKH signaling. *Proceedings of the National Academy of Sciences*, 111(22): 8137–8142.

Wei, M., S. Brandhorst, M. Shelehchi, H. Mirzaei, C. W. Cheng, J. Budniak, S. Groshen, W. J. Mack, E. Guen and

S. Di Biase (2017). Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Science translational medicine*, 9(377): eaai8700.

Wiley, C. D. and J. Campisi (2016). From ancient pathways to aging cells—connecting metabolism and cellular senescence. *Cell metabolism*, 23(6): 1013–1021.

Wood, J. G. and S. L. Helfand (2013). Chromatin structure and transposable elements in organismal aging. *Frontiers in genetics*, 4: 274.

Wu, J. J., J. Liu, E. B. Chen, J. J. Wang, L. Cao, N. Narayan, M. M. Fergusson, I. I. Rovira, M. Allen and D. A. Springer (2013). Increased mammalian lifespan and a segmental and tissue-specific slowing of aging after genetic reduction of mTOR expression. *Cell reports*, 4(5): 913–920.

Xu, J., G. Gontier, Z. Chaker, P. Lacube, J. Dupont and M. Holzenberger (2014). Longevity effect of IGF-1R+/− mutation depends on genetic background-specific receptor activation. *Aging cell*, 13(1): 19–28.

Yan, L., D. E. Vatner, J. P. O'Connor, A. Ivessa, H. Ge, W. Chen, S. Hirotani, Y. Ishikawa, J. Sadoshima, and S. F. Vatner (2007). Type 5 adenylyl cyclase disruption increases longevity and protects against stress. *Cell*, 130(2): 247–258.

Yanai, H., A. Budovsky, T. Barzilay, R. Tacutu and V. E. Fraifeld (2017). Wide-scale comparative analysis of longevity genes and interventions. *Aging Cell*, 16(6): 1267–1275.

Yang, X., T. A. Doser, C. X. Fang, J. M. Nunn, R. Janardhanan, M. Zhu, N. Sreejayan, M. T. Quinn and J. Ren (2006). Metallothionein prolongs survival and antagonizes senescence-associated cardiomyocyte diastolic dysfunction: role of oxidative stress. *The FASEB Journal*, 20(7): 1024–1026.

Zhang, G., J. Li, S. Purkayastha, Y. Tang, H. Zhang, Y. Yin, B. Li, G. Liu and D. Cai (2013). Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GnRH. *Nature*, 497(7448): 211–216.

Zhang, H., K. J. A. Davies and H. J. Forman (2015). Oxidative stress response and Nrf2 signaling in aging. *Free Radical Biology and Medicine*, 88: 314–336.

Zhang, Y., Y. Xie, E. D. Berglund, K. C. Coate, T. T. He, T. Katafuchi, G. Xiao, M. J. Potthoff, W. Wei and Y. Wan (2012). The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. e*life*, 1: e00065.

Zheng, S., E. B. D. S. Clabough, Sarkar, Futter, D. C. Rubinsztein and S. O. Zeitlin (2010). Deletion of the huntingtin polyglutamine stretch enhances neuronal autophagy and longevity in mice. *PLoS genetics*, 6(2): e1000838.

Zid, B. M., A. N. Rogers, S. D. Katewa, M. A. Vargas, M. C. Kolipinski, T. A. Lu, S. Benzer and P. Kapahi (2009). 4E-BP extends lifespan upon dietary restriction by enhancing mitochondrial activity in Drosophila. *Cell*, 139(1): 149–160.

Zordan, M. A., P. Cisotto, C. Benna, A. Agostino, G. Rizzo, A. Piccin, M. Pegoraro, F. Sandrelli, G. Perini and G. Tognon (2006). Post-transcriptional silencing and functional characterization of the Drosophila melanogaster homolog of human Surf1. *Genetics*, 172(1): 229–241.

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