Immortality Research Literatures

Mark Herbert

World Development Institute
39-06 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

Abstract: Immortality is eternal life, being exempt from death; unending existence. Some modern species may possess biological immortality. Certain scientists, futurists, and philosophers have theorized about the immortality of the human body, with some suggesting that human immortality may be achievable in the first few decades of the 21st century. Other advocates believe that life extension is a more achievable goal in the short term, with immortality awaiting further research breakthroughs. The absence of ageing would provide humans with biological immortality, but not invulnerability to death by disease or physical trauma; although mind uploading could solve that if it proved possible. Whether the process of internal endoimmortality is delivered within the upcoming years depends chiefly on research (and in neuron research in the case of endoimmortality through an immortalized cell line) in the former view and perhaps is an awaited goal in the latter case. What form an unending human life would take, or whether an immaterial soul exists and possesses immortality, has been a major point of focus of religion, as well as the subject of speculation and debate. In religious contexts, immortality is often stated to be one of the promises of divinities to human beings who perform virtue or follow divine law. This article introduces recent research reports as references in the related studies.
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Introduction

Immortality is eternal life, being exempt from death; unending existence. Some modern species may possess biological immortality. Certain scientists, futurists, and philosophers have theorized about the immortality of the human body, with some suggesting that human immortality may be achievable in the first few decades of the 21st century. Other advocates believe that life extension is a more achievable goal in the short term, with immortality awaiting further research breakthroughs. The absence of ageing would provide humans with biological immortality, but not invulnerability to death by disease or physical trauma; although mind uploading could solve that if it proved possible. Whether the process of internal endoimmortality is delivered within the upcoming years depends chiefly on research (and in neuron research in the case of endoimmortality through an immortalized cell line) in the former view and perhaps is an awaited goal in the latter case. What form an unending human life would take, or whether an immaterial soul exists and possesses immortality, has been a major point of focus of religion, as well as the subject of speculation and debate. In religious contexts, immortality is often stated to be one of the promises of divinities to human beings who perform virtue or follow divine law. (https://en.wikipedia.org/wiki/Immortality). This article introduces recent research reports as references in the related studies.

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Adolphe, M. and S. Thenet (1990). "[The concept of cellular immortality, a myth or a reality. Example of "immortalized" articular chondrocytes]." Bull Acad Natl Med 174(1): 139-144; discussion 144-136.

The concept of cellular immortality, which arose from the historical studies of A. Carrel, is getting a new start with the progress of virology. However, the definition of cell immortalization is still ambiguous. Although scientists agree that cells regarded as immortal have acquired an infinite growth capacity, the relationship of this change with the first stages of transformation is difficult to clearly define. Immortalized cell lines have already been obtained from numerous cell types by using viral infection or transfection with viral and cellular genes. Immortalization of cells is interesting for three main reasons: it permits study of the steps in progression to transformation, allows establishment of cell lines for producing biological products, and permits various cell types to maintain a part of their differentiated functions. For example, hypothalamic neurosecretory cells, macrophages, astrocytes and intestinal epithelial cells have been immortalized and these lines can be used for understanding the balance between division and differentiation, and also for pharmacotoxicological studies. In our laboratory, we immortalized rabbit articular chondrocytes by transfection with SV40 large T and little t encoding genes. At the 9th subculture, when the control culture was senescent, clones of

polygonal cells appeared in the transfected cell cultures. Three clones have been selected and have been maintained in culture for two years. Growth curves of normal and SV40-transfected chondrocytes were compared and displayed similar doubling times (approximately 20 hours). The exponential phase of growth was longer for immortalized cells resulting in a 2-fold higher saturation density. These cells appear to be not fully transformed and maintain some properties of differentiated chondrocytes.(ABSTRACT TRUNCATED AT 250 WORDS)

Ahmed, S. (2006). "Uncoupling of pathways that promote postmitotic life span and apoptosis from replicative immortality of Caenorhabditis elegans germ cells." Aging Cell 5(6): 559-563.

A dichotomy exists between germ and somatic cells in most organisms, such that somatic cell lineages proliferate for a single generation, whereas the germ cell lineage has the capacity to proliferate from one generation to the next, indefinitely. Several theories have been proposed to explain the unlimited replicative life span of germ cells, including the elimination of damaged germ cells by apoptosis or expression of high levels of gene products that prevent aging in somatic cells. These theories were tested in the nematode Caenorhabditis elegans by examining the consequences of eliminating either apoptosis or the daf-16, daf-18 or sir-2.1 genes that promote longevity of postmitotic somatic cells. However, germ cells of strains deficient for these activities displayed an unlimited proliferative capacity. Thus, C. elegans germ cells retain their youthful character via alternative pathways that prevent or eliminate damage that accumulates as a consequence of cell proliferation.

Ahmed, S. and J. Hodgkin (2000). "MRT-2 checkpoint protein is required for germline immortality and telomere replication in C. elegans." Nature 403(6766): 159-164.

The germ line is an immortal cell lineage that is passed indefinitely from one generation to the next. To identify the genes that are required for germline immortality, we isolated Caenorhabditis elegans mutants with mortal germ lines--worms that can reproduce for several healthy generations but eventually become sterile. One of these mortal germline (mrt) mutants, mrt-2, exhibits progressive telomere shortening and accumulates end-to-end chromosome fusions in later generations, indicating that the MRT-2 protein is required for telomere replication. In addition, the germ line of mrt-2 is hypersensitive to X-rays and to transposon activity. Therefore, mrt-2 has defects in responding both to damaged DNA and to normal double-strand breaks present at telomeres. mrt-2 encodes a homologue of a checkpoint gene that is required to sense DNA damage in yeast. These results indicate that telomeres may be identified as a type of DNA damage and then repaired by the telomere-replication enzyme telomerase.

Antal, T., et al. (2007). "Aging and immortality in a cell proliferation model." J Theor Biol 248(3): 411-417.

We investigate a model of cell division in which the length of telomeres within a cell regulates its proliferative potential. At each division, telomeres undergo a systematic length decrease as well as a superimposed fluctuation due to exchange of telomere DNA between the two daughter cells. A cell becomes senescent when one or more of its telomeres become shorter than a critical length. We map this telomere dynamics onto a biased branching-diffusion process with an absorbing boundary condition whenever any telomere reaches the critical length. Using first-passage ideas, we find a phase transition between finite lifetime and immortality (infinite proliferation) of the cell population as a function of the influence of telomere shortening, fluctuations, and cell division.

Arlow, J. A. (1982). "Scientific cosmogony, mythology, and immortality." Psychoanal Q 51(2): 177-195.

Some current scientific theories of cosmogony demonstrate significant similarities to the cosmological theories of mythology and of certain religions. The notion that the universe originated in a specific cataclysmic explosion raises the mental construct of a center of the universe. This concept plays an important role in mythology and is related to the idea of the cyclical renewal of time. Such concepts, both scientific and mythological, serve as reassurance against the fear of extinction. Aspirations to immortality re-emerge in disguised form in the search for life elsewhere in the universe. Some of the cosmological theories resemble metaphorical elaborations of childhood concepts of procreation.

Arnett, W. S. (1991). "Growing old in the cradle: old age and immortality among the kings of ancient Assyria." Int J Aging Hum Dev 32(2): 135-141.

The desire for a long and healthy life was expressed often by Assyrian kings in their extant public texts from the 14th through the 7th centuries BC. But advanced old age, whether for monarchs or commoners, was not achieved very often in the ancient world. Consequently, Assyrian royal inscriptions frequently reflect concern for another kind of longevity--an immortality achieved by having one's works and one's name preserved and remembered by posterity. Almost every dedicatory inscription associated with public works--palaces, temples, etc.--expressed the importance of these kings' participation in what this writer terms a "family cult." The latter constituted a sense of continuity from father to son to grandson, and so on, which depended upon each new generation to preserve and/or restore the works and the "names" of their predecessors. If the Assyrian kings each did their job as "Curator" or "Steward" of the family's heritage,

they expressed the hope that they would not be forgotten--perhaps the closest they could get to achieving immortality.

Banerjee, M. (2020). ""Life Is So Good": Centenarians' Autobiographies Between the Promise of Immortality and the Specter of Death." Omega (Westport): 30222820966940.

When we are trying to come to terms with death and dying, or the loss of a loved one, cultural practices can fulfill important functions. Literature, music, and the arts can help us cope with loss by expressing our emotions in a way which seems to be universal. This paper investigates the role of co-written centenarians' autobiographies in this context. It focuses specifically on autobiographies by African American centenarians and white co-authors. The article investigates the dialogue between the centenarian and the co-author as a ritual for coming to terms with the co-author's fear of mortality. It argues that for a white readership that defines itself as secular, the black centenarian - deeply religious himself - can serve as a surrogate and a role model. Just as he assures his middle-aged, white co-author that death is not to be feared, his autobiography may offer a secular readership a model for dying.

Bell, R. J., et al. (2016). "Understanding TERT Promoter Mutations: A Common Path to Immortality." Mol Cancer Res 14(4): 315-323.

Telomerase (TERT) activation is a fundamental step in tumorigenesis. By maintaining telomere length, telomerase relieves a main barrier on cellular lifespan, enabling limitless proliferation driven by oncogenes. The recently discovered, highly recurrent mutations in the promoter of TERT are found in over 50 cancer types, and are the most common mutation in many cancers. Transcriptional activation of TERT, via promoter mutation or other mechanisms, is the rate-limiting step in production of active telomerase. Although TERT is expressed in stem cells, it is naturally silenced upon differentiation. Thus, the presence of TERT promoter mutations may shed light on whether a particular tumor arose from a stem cell or more differentiated cell type. It is becoming clear that TERT mutations occur early during cellular transformation, and activate the TERT promoter by recruiting transcription factors that do not normally regulate TERT gene expression. This review highlights the fundamental and widespread role of TERT promoter mutations in tumorigenesis, including recent progress on their mechanism of transcriptional activation. These somatic promoter mutations, along with germline variation in the TERT locus also appear to have significant value as biomarkers of patient outcome. Understanding the precise molecular mechanism of TERT activation by promoter mutation and germline variation may inspire novel cancer cell-specific targeted therapies for a large number of cancer patients.

Bhar, G. C. (2016). "In Search of Rationality in Human Longevity and Immortality." Mens Sana Monogr 14(1): 187-213.

The human body is machine-like, but self-moving, self-regulating, and self-adjusting, governed by willpower and intelligence. Aging of the body is basically a maintenance problem and so it could perhaps be postponed by thorough and frequent maintenance. Aging brings on a cascade of ills and health problems leading to deterioration of physical, mental, emotional, and social dimensions of life. This paper deals with solution of the problem philosophically in the light of Indian scriptures without entering into traditional bioethical issues. With a meaningful reason for existence, life can be extended. Examining the scientific perspectives on aging, some common manipulations for its extension are discussed. These are calorie restriction, vitamin and antioxidant treatment, exercise and hormonal interventions, etc. Finally, the question of longevity is explored through pursuance of eternal value-based activity and spirituality in the tradition of Indian heritage.

Bignold, L. P. (2007). "Variation, "evolution", immortality and genetic instabilities in tumour cells." Cancer Lett 253(2): 155-169.

The pathological characteristics of tumour cells often include variation of their histopathological features (i.e. "degrees of de-differentiation") between cases of the same tumour type and between different foci within individual tumours. Usually, only a few cell lines from tumours are immortal. Currently, somatic mutation, replicative infidelity of DNA and aneuploidy are suggested as alternative mechanisms of genomic disturbance underlying tumours. Nevertheless, apart from Hansemann's ideas of "anaplasia" and "de-differentiation" (proposed in the 1890s), and supposed "evolutionary themes" in cancer cell biology, little has been published concerning how histopathologic variation and immortality in tumour cells might arise. This paper reviews applications of the concepts of "variation" to tumours, including concepts of "evolution" and "cellular Darwinism". It is proposed that combinations of somatic mutation, DNA replicative infidelity and aneuploidy may explain the variabilities in tumours, and provide immortality in occasional tumour cells. A possible model involves (i) an initial somatic mutation causing reduced replicative fidelity of DNA, which could be variable in intensity, and thus give rise to variations between cases; (ii) a phase of replicative infidelity of DNA causing daughter cells lines to develop various abnormalities to different degrees, and hence provide for variation between areas

of the same tumour. As a last event (iii) occasional asymmetric chromosomal distributions (aneuploidy) might "refresh" the ability of a daughter cell to replicate DNA faithfully causing them to become immortal. Thus extensively mutant and variable, hyperploid, and occasionally immortal cells might arise.

Billmyre, K. K., et al. (2019). "The meiotic phosphatase GSP-2/PP1 promotes germline immortality and small RNA-mediated genome silencing." PLoS Genet 15(3): e1008004.

Germ cell immortality, or transgenerational maintenance of the germ line, could be promoted by mechanisms that could occur in either mitotic or meiotic germ cells. Here we report for the first time that the GSP-2 PP1/Glc7 phosphatase promotes germ cell immortality. Small RNA-induced genome silencing is known to promote germ cell immortality, and we identified a separation-of-function allele of C. elegans gsp-2 that is compromised for germ cell immortality and is also defective for small RNA-induced genome silencing and meiotic but not mitotic chromosome segregation. Previous work has shown that GSP-2 is recruited to meiotic chromosomes by LAB-1, which also promoted germ cell immortality. At the generation of sterility, gsp-2 and lab-1 mutant adults displayed germline degeneration, univalents, histone methylation and histone phosphorylation defects in oocytes, phenotypes that mirror those observed in sterile small RNA-mediated genome silencing mutants. Our data suggest that a meiosis-specific function of GSP-2 ties small RNA-mediated silencing of the epigenome to germ cell immortality. We also show that transgenerational epigenomic silencing at hemizygous genetic elements requires the GSP-2 phosphatase, suggesting a functional link to small RNAs. Given that LAB-1 localizes to the interface between homologous chromosomes during pachytene, we hypothesize that small localized discontinuities at this interface could promote genomic silencing in a manner that depends on small RNAs and the GSP-2 phosphatase.

Blagosklonny, M. V. (2006). "Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition." Cell Cycle 5(18): 2087-2102.

While ruling out programmed aging, evolutionary theory predicts a quasi-program for aging, a continuation of the developmental program that is not turned off, is constantly on, becoming hyper-functional and damaging, causing diseases of aging. Could it be switched off pharmacologically? This would require identification of a molecular target involved in cell senescence, organism aging and diseases of aging. Notably, cell senescence is associated with activation of the TOR (target of rapamycin) nutrient- and mitogen-sensing pathway, which promotes cell growth, even though cell cycle is blocked. Is TOR involved in organism aging? In fact, in yeast (where the cell is the organism), caloric restriction, rapamycin and mutations that inhibit TOR all slow down aging. In animals from worms to mammals caloric restrictions, life-extending agents, and numerous mutations that increase longevity all converge on the TOR pathway. And, in humans, cell hypertrophy, hyper-function and hyperplasia, typically associated with activation of TOR, contribute to diseases of aging. Theoretical and clinical considerations suggest that rapamycin may be effective against atherosclerosis, hypertension and hyper-coagulation (thus, preventing myocardial infarction and stroke), osteoporosis, cancer, autoimmune diseases and arthritis, obesity, diabetes, macula-degeneration, Alzheimer's and Parkinson's diseases. Finally, I discuss that extended life span will reveal new causes for aging (e.g., ROS, 'wear and tear', Hayflick limit, stem cell exhaustion) that play a limited role now, when quasi-programmed senescence kills us first.

Bronstein, C. (2002). "Borges, immortality and the circular ruins." Int J Psychoanal 83(Pt 3): 647-660.

The author explores ideas surrounding immortality and death focusing on the interplay between their development in two stories by Borges ('The circular ruins' and 'The immortal') and their manifestation in a patient. With the help of Borges's stories, the author addresses the desperate necessity experienced by some individuals to search for immortality. This is not just an expression of the universal wish to live forever but, at a deeper level, arises from the impossibility of bearing the mental pain of experiencing ordinary human vulnerability and loss - death being the ultimate expression of such vulnerability. It is suggested that the relentless pursuit of immortality in such individuals expresses an omnipotent phantasy of ridding the self of the emotional pain and fear that arises through being alive. It leads to a denial of the emotional significance of passage of time, of separation and sexual differences. In actuality, the individual's state of not feeling approximates to a complete loss of human identity and emotional death, with no place for any meaningful others. The individual him/herself becomes a 'mere image', living in a delusional world peopled by him/herself and his/ her projections, and ending up trapped inside the circular ruins he/she has generated. The horror experienced at the stark awareness of the individual's emotional death and the wish to re-establish contact with the good internal objects that have been attacked sets in motion the long process of searching for the recovery of a sense of temporality (that would still include the wish for immortality) and, with it, a sense of identity.

Buckley, B. A., et al. (2012). "A nuclear Argonaute promotes multigenerational epigenetic inheritance and germline immortality." Nature 489(7416): 447-451.

Epigenetic information is frequently erased

near the start of each new generation. In some cases, however, epigenetic information can be transmitted from parent to progeny (multigenerational epigenetic inheritance). A particularly notable example of this type of epigenetic inheritance is double-stranded RNA-mediated gene silencing in Caenorhabditis elegans. This RNA-mediated interference (RNAi) can be inherited for more than five generations. To understand this process, here we conduct a genetic screen for nematodes defective in transmitting RNAi silencing signals to future generations. This screen identified the heritable RNAi defective 1 (hrde-1) gene. hrde-1 encodes an Argonaute protein that associates with small interfering RNAs in the germ cells of progeny of animals exposed to double-stranded RNA. In the nuclei of these germ cells, HRDE-1 engages the nuclear RNAi defective pathway to direct the trimethylation of histone H3 at Lys 9 (H3K9me3) at RNAi-targeted genomic loci and promote RNAi inheritance. Under normal growth conditions, HRDE-1 associates with endogenously expressed short interfering RNAs, which direct nuclear gene silencing in germ cells. In hrde-1- or nuclear RNAi-deficient animals, germline silencing is lost over generational time. Concurrently, these animals exhibit steadily worsening defects in gamete formation and function that ultimately lead to sterility. These results establish that the Argonaute protein HRDE-1 directs gene-silencing events in germ-cell nuclei that drive multigenerational RNAi inheritance and promote immortality of the germ-cell lineage. We propose that C. elegans use the RNAi inheritance machinery to transmit epigenetic information, accrued by past generations, into future generations to regulate important biological processes.

Carnero, A., et al. (2015). "Disruptive chemicals, senescence and immortality." Carcinogenesis 36 Suppl 1: S19-37.

Carcinogenesis is thought to be a multistep process, with clonal evolution playing a central role in the process. Clonal evolution involves the repeated 'selection and succession' of rare variant cells that acquire a growth advantage over the remaining cell population through the acquisition of 'driver mutations' enabling a selective advantage in a particular micro-environment. Clonal selection is the driving force behind tumorigenesis and possesses three basic requirements: (i) effective competitive proliferation of the variant clone when compared with its neighboring cells, (ii) acquisition of an indefinite capacity for self-renewal, and (iii) establishment of sufficiently high levels of genetic and epigenetic variability to permit the emergence of rare variants. However, several questions regarding the process of clonal evolution remain. Which cellular processes initiate carcinogenesis in the first place? To what extent are environmental carcinogens responsible for the initiation of clonal evolution? What are the roles of genotoxic and non-genotoxic carcinogens in carcinogenesis? What are the underlying mechanisms responsible for chemical carcinogen-induced cellular immortality? Here, we explore the possible mechanisms of cellular immortalization, the contribution of immortalization to tumorigenesis and the mechanisms by which chemical carcinogens may contribute to these processes.

Chen, X., et al. (2014). "Tumor viruses and replicative immortality--avoiding the telomere hurdle." Semin Cancer Biol 26: 43-51.

Tumor viruses promote cell proliferation in order to gain access to an environment suitable for persistence and replication. The expression of viral products that promote growth transformation is often accompanied by the induction of multiple signs of telomere dysfunction, including telomere shortening, damage of telomeric DNA and chromosome instability. Long-term survival and progression to full malignancy require the bypassing of senescence programs that are triggered by the damaged telomeres. Here we review different strategies by which tumor viruses interfere with telomere homeostasis during cell transformation. This frequently involves the activation of telomerase, which assures both the integrity and functionality of telomeres. In addition, recent evidence suggests that oncogenic viruses may activate a recombination-based mechanism for telomere elongation known as Alternative Lengthening of Telomeres (ALT). This error-prone strategy promotes genomic instability and could play an important role in viral oncogenesis.

Chiu, C. P. and C. B. Harley (1997). "Replicative senescence and cell immortality: the role of telomeres and telomerase." Proc Soc Exp Biol Med 214(2): 99-106.

Telomere shortening is correlated with cell senescence in vitro and cell aging in vivo. The telomere hypothesis suggests that telomere length serves as a mitotic clock for timing cellular replicative life span. Expression of telomerase stabilizes telomere length and allows for continual replication, or cell immortality. This article reviews recent evidences for the role of telomere length and telomerase in the regulation of cellular replicative life span. The therapeutic potential of manipulating telomerase expression and telomere length is also discussed.

Colarusso, C. A. (2011). "Death, rejuvenation and immortality in film: On Golden Pond (1981), Cat on a Hot Tin Roof (1958) and Cocoon (1985)." Am J Psychoanal 71(2): 146-161.

This paper seeks to highlight the developmental tasks of late adulthood with the help of three Hollywood movies. These tasks include: (i) struggling to maintain physical integrity, (ii) handling the "wound of mortality", (iii) maintaining activity and sexuality, and (iv) becoming wise. Among other

challenges faced by an individual during this phase of life are loss of love objects, illness and possible compromise of mental functions, de-cathexis of material possessions and coming to terms with one's approaching death. All sorts of healthy and unhealthy psychosocial maneuvers come to the surface as a result of these stresses. This paper illustrates these dilemmas and their potential solutions via a discussion of three movies.

Conn, R., et al. (1996). "Reduction of anxiety about death: need for beliefs about immortality." Psychol Rep 79(3 Pt 2): 1315-1318.

It was hypothesized that individuals who are reminded of their own mortality will experience anxiety which is reduced by an increased need for belief in immortality. A questionnaire assessing the need for literal and two forms of symbolic immortality was developed. Analysis showed that awareness of mortality increased scores on the need for literal immortality but not on either form of symbolic immortality.

Crocker, J. (2001). "Telomeres and telomerases: intimations of immortality." Eur J Gastroenterol Hepatol 13(8): 889-890.

There is a constant balance in cancer cells between division and death. The malignant phenotype is associated with a continuing cell cycle or 'immortalization'. Telomeres, structures that cap the chromosomes, are related to cell longevity and are regulated by a ribonucleoprotein called telomerase. This review describes the possible roles of telomeres and telomerase in the malignant process.

Cullivan, R. and B. A. Lawlor (2002). "A delusion of immortality - the dilemma of the Struldbruggs." Ir J Psychol Med 19(1): 32-34.

We describe a lady with a history of recurrent psychotic depression, together with a persistent delusion of immortality, which appears to be independent of the depressive illness. It is of interest that this woman is a patient of the hospital founded by Dean Jonathan Swift, who described a people stricken with a similar dilemma of unhappy immortality over 200 years ago.

Dalerba, P., et al. (2005). "Reconstitution of human telomerase reverse transcriptase expression rescues colorectal carcinoma cells from in vitro senescence: evidence against immortality as a constitutive trait of tumor cells." Cancer Res 65(6): 2321-2329.

Although in vitro establishment of new colorectal carcinoma (CRC) cell lines is an infrequent event, we have observed that primary cultures of CRC can be repeatedly and reproducibly initiated following in vitro plating of tumor-derived epithelial cells. These cultures, however, usually display a short life span as they undergo a limited number of cell passages before entering a state of irreversible growth arrest. In this study, we show that short-lived CRC primary cultures lack constitutive telomerase activity and undergo a senescence process characterized by progressive telomere shortening. Moreover, transduction of these cells with a retroviral vector encoding human telomerase reverse transcriptase (hTERT) is sufficient to reconstitute telomerase activity and allow immortalization. Detailed molecular characterization of hTERT-immortalized CRC cell lines confirms their individual tumor origin by showing expression of colonic epithelial differentiation markers, such as cytokeratin-20 (CK20), full match with class I and class II human leukocyte antigen genotyping of autologous B-lymphoblastoid cells, and presence of somatic mutations in key cancer genes (KRAS2, APC) identical to those of the corresponding autologous original tumor tissues. Moreover, functional characterization of hTERT-immortalized CRC cell lines shows that they have a transformed phenotype, being able to form colonies in soft agar and tumors in severe combined immunodeficient mice. Most interestingly, immunohistochemical analysis of original tumor tissues indicates that short-lived CRC primary cultures, although hTERT-negative in vitro, derive from hTERT-positive tumors. Taken together, our data show that, in a least subset of CRC, biochemical pathways involved in maintenance of telomere length, such as telomerase, are not activated in a constitutive way in all tumor cells.

Danchin, A. (2009). "Natural selection and immortality." Biogerontology 10(4): 503-516.

Genomes replicate while the host cells reproduce. I explore the reproduction/replication dialogue, based on a deep analysis of bacterial genomes, in relation to ageing. Making young structures from aged ones implies creating information. I revisit Information Theory, showing that the laws of physics permit de novo creation of information, provided an energy-dependent process preserving functional entities makes room for entities accumulating information. I identify explicit functions involved in the process and characterise some of their genes. I suggest that the energy source necessary to establish reproduction while replication is temporarily stopped could be the ubiquitous polyphosphates. Finally, I show that rather than maintain and repair the original individual, organisms tend to metamorphose into young ones, sometimes totally, sometimes progressively. This permits living systems to accumulate information over generations, but has the drawback, in multicellular organisms, to open the door for immortalisation, leading to cancer.

Day, K. C., et al. (2002). "Rescue of embryonic epithelium reveals that the homozygous deletion of the retinoblastoma gene confers growth factor independence and immortality but does not influence epithelial differentiation or tissue morphogenesis." J

Biol Chem 277(46): 44475-44484.

The ability to rescue viable prostate precursor tissue from retinoblastoma-deficient (Rb-/-) fetal mice has allowed for the isolation and characterization of the first Rb-/- prostate epithelial cell line. This cell line, designated Rb-/-PrE, was utilized for experiments examining the consequences of Rb loss on an epithelial population. These findings demonstrated that Rb deletion has no discernible effect on prostatic histodifferentiation in Rb-/-PrE cultures. When Rb-/-PrE cells were recombined with embryonic rat urogenital mesenchyme and implanted into athymic male, nude mouse hosts, the recombinants developed into fully differentiated and morphologically normal prostate tissue. The Rb-/-PrE phenotype was characterized by serum independence in culture and immortality in vivo, when compared with wild type controls. Cell cycle analysis revealed elevated S phase DNA content accompanied by increased expression of cyclin E1 and proliferating cell nuclear antigen. Rb-/-PrE cultures also exhibited a diminished ability to growth arrest under high density culture conditions. We believe that the development of Rb-/- prostate tissue and cell lines has provided a unique experimental platform with which to investigate the consequences of Rb deletion in epithelial cells under various physiological conditions. Additionally, the development of this technology will allow similar studies in other tissues and cell populations rescued from Rb-/- fetuses.

de Caralt, S., et al. (2007). "Cell culture from sponges: pluripotency and immortality." Trends Biotechnol 25(10): 467-471.

Sponges are a source of compounds with potential pharmaceutical applications. In this article, methods of sponge cell culture for production of these bioactive compounds are reviewed, and new approaches for overcoming the problem of metabolite supply are examined. The use of embryos is proposed as a new source of sponge material for cell culture. Stem cells are present in high amounts in embryos and are more versatile and resistant to infections than adult cells. Additionally, genetic engineering and cellular research on apoptotic mechanisms are promising new fields that might help to improve cell survival in sponge-cell lines. We propose that one topic for future research should be how to reduce apoptosis, which appears to be very high in sponge cell cultures.

Dechesne, M., et al. (2003). "Literal and symbolic immortality: the effect of evidence of literal immortality on self-esteem striving in response to mortality salience." J Pers Soc Psychol 84(4): 722-737.

Three studies investigated the effect of encouraging participants to believe in an afterlife on the relationship between mortality salience and self-esteem striving. Participants were exposed to essays arguing either in favor of or against the existence of an afterlife, and reminded about death or a control topic. Mortality salience led to increased accuracy ratings of a positive personality description (Studies 1 and 2) and increased striving for and defense of values (Study 3) among participants who read the essay arguing against an afterlife, but not among participants who read the essay in favor of it. The implications for the terror management analysis of self-esteem, the appeal of immortality beliefs, and the interplay between self-esteem striving and spiritual pursuits are discussed.

Derventzi, A., et al. (1996). "Molecular links between cellular mortality and immortality (review)." Anticancer Res 16(5A): 2901-2910.

Normal diploid cells cultivated in vitro exhibit limited division potential while undergoing ageing during serial passaging. In contrast, cells that have been genetically transformed appear to have lost the regulatory mechanisms of limited growth potential and may continue to divide indefinitely. While cellular mortality is characterised by a progressive cessation of cell growth manifested in cell culture by senescence, immortalisation is the escape from senescence as a result of multiple mechanisms involving the inactivation of tumour suppressor genes, the elevated expression of oncogenes, as well as other genetic and epigenetic changes. The mechanisms governing mortality and immortality are fundamentally linked. The physiological and biochemical features which characterise cellular mortality are examined, herein in the search for markers and timing mechanisms of mortality. The genetic elements involved in the control of mortality and immortality are also discussed, and the fundamental similarities between the molecular and genetic aspects which govern the determination of the phenotypes manifesting the two processes are underlined.

Dilmac, J. A. (2018). "Martyrs Never Die: Virtual Immortality of Turkish Soldiers." Omega (Westport) 78(2): 161-177.

The new technologies have changed the rituals related to death: Creation of memorial webpages and of virtual tombs, celebration of death anniversaries are now common currency on the Internet. In spite of their disappearance among the living, the deceased continue to exist on the Web. They still receive messages from their relatives but also from strangers and are at the heart of discussions, prolonging their presence. New technologies have led to a new concept of time and of "where life ends." Through the analysis of Facebook's accounts devoted to Turkish martyrs, this article aimed to describe the new funeral rituals seen on the Internet.

Dou, X., et al. (2020). "Evidence for immortality and autonomy in animal cancer models is often not provided, which causes confusion on key issues of cancer biology." J Cancer 11(10): 2887-2920.

Modern research into carcinogenesis has undergone three phases. Surgeons and pathologists started the first phase roughly 250 years ago, establishing morphological traits of tumors for pathologic diagnosis, and setting immortality and autonomy as indispensable criteria for neoplasms. A century ago, medical doctors, biologists and chemists started to enhance "experimental cancer research" by establishing many animal models of chemical-induced carcinogenesis for studies of cellular mechanisms. In this second phase, the two-hit theory and stepwise carcinogenesis of "initiation-promotion" or "initiation-promotion-progression" were established, with an illustrious finding that outgrowths induced in animals depend on the inducers, and thus are not authentically neoplastic, until late stages. The last 40 years are the third incarnation, molecular biologists have gradually dominated the carcinogenesis research fraternity and have established numerous genetically-modified animal models of carcinogenesis. However, evidence has not been provided for immortality and autonomy of the lesions from most of these models. Probably, many lesions had already been collected from animals for analyses of molecular mechanisms of "cancer" before the lesions became autonomous. We herein review the monumental work of many predecessors to reinforce that evidence for immortality and autonomy is essential for confirming a neoplastic nature. We extrapolate that immortality and autonomy are established early during sporadic human carcinogenesis, unlike the late establishment in most animal models. It is imperative to resume many forerunners' work by determining the genetic bases for initiation, promotion and progression, the genetic bases for immortality and autonomy, and which animal models are, in fact, good for identifying such genetic bases.

Drolet, J. L. (1990). "Transcending death during early adulthood: symbolic immortality, death anxiety, and purpose in life." J Clin Psychol 46(2): 148-160.

Robert Jay Lifton has originated a comprehensive theory of development based on the human psychobiological need to symbolize death and life continuity. He calls this condition the sense of symbolic immortality and argues that life is threatened whenever death is not transcended. A Sense of Symbolic Immortality Scale was built and administered to two groups of young adults (N = 136) in order to test the hypothesis that symbolic immortality develops with age (Drolet, 1986). Templer's Death Anxiety Scale and Crumbaugh and Maholick's Purpose in Life Test also were administered. Results show that established adults have a sense of symbolic immortality and a purpose in life significantly stronger than those of young adults. They show a negative relation between death anxiety and purpose in life, while purpose in life correlates highly with the sense of symbolic immortality. Finally, the premise that the sense of symbolic immortality helps cope with the fear of death is supported.

Duesberg, P. and A. McCormack (2013). "Immortality of cancers: a consequence of inherent karyotypic variations and selections for autonomy." Cell Cycle 12(5): 783-802.

Immortality is a common characteristic of cancers, but its origin and purpose are still unclear. Here we advance a karyotypic theory of immortality based on the theory that carcinogenesis is a form of speciation. Accordingly, cancers are generated from normal cells by random karyotypic rearrangements and selection for cancer-specific reproductive autonomy. Since such rearrangements unbalance long-established mitosis genes, cancer karyotypes vary spontaneously but are stabilized perpetually by clonal selections for autonomy. To test this theory we have analyzed neoplastic clones, presumably immortalized by transfection with overexpressed telomerase or with SV40 tumor virus, for the predicted clonal yet flexible karyotypes. The following results were obtained: (1) All immortal tumorigenic lines from cells transfected with overexpressed telomerase had clonal and flexible karyotypes; (2) Searching for the origin of such karyotypes, we found spontaneously increasing, random aneuploidy in human fibroblasts early after transfection with overexpressed telomerase; (3) Late after transfection, new immortal tumorigenic clones with new clonal and flexible karyotypes were found; (4) Testing immortality of one clone during 848 unselected generations showed the chromosome number was stable, but the copy numbers of 36% of chromosomes drifted +/- 1; (5) Independent immortal tumorigenic clones with individual, flexible karyotypes arose after individual latencies; (6) Immortal tumorigenic clones with new flexible karyotypes also arose late from cells of a telomerase-deficient mouse rendered aneuploid by SV40 virus. Because immortality and tumorigenicity: (1) correlated exactly with individual clonal but flexible karyotypes; (2) originated simultaneously with such karyotypes; and (3) arose in the absence of telomerase, we conclude that clonal and flexible karyotypes generate the immortality of cancers.

Durant, S. T. (2012). "Telomerase-independent paths to immortality in predictable cancer subtypes." J Cancer 3: 67-82.

The vast majority of cancers commandeer the activity of telomerase - the remarkable enzyme responsible for prolonging cellular lifespan by maintaining the length of telomeres at the ends of chromosomes. Telomerase is only normally active in embryonic and highly proliferative somatic cells. Thus, targeting telomerase is an attractive anti-cancer therapeutic rationale currently under investigation in various phases of clinical development. However, previous reports suggest that an average of 10-15% of

all cancers lose the functional activity of telomerase and most of these turn to an Alternative Lengthening of Telomeres pathway (ALT). ALT-positive tumours will therefore not respond to anti-telomerase therapies and there is a real possibility that such drugs would be toxic to normal telomerase-utilising cells and ultimately select for resistant cells that activate an ALT mechanism. ALT exploits certain DNA damage response (DDR) components to counteract telomere shortening and rapid trimming. ALT has been reported in many cancer subtypes including sarcoma, gastric carcinoma, central nervous system malignancies, subtypes of kidney (Wilm's Tumour) and bladder carcinoma, mesothelioma, malignant melanoma and germ cell testicular cancers to name but a few. A recent heroic study that analysed ALT in over six thousand tumour samples supports this historical spread, although only reporting an approximate 4% prevalence. This review highlights the various methods of ALT detection, unravels several molecular ALT models thought to promote telomere maintenance and elongation, spotlights the DDR components known to facilitate these and explores why certain tissues are more likely to subvert DDR away from its usually protective functions, resulting in a predictive pattern of prevalence in specific cancer subsets.

Edington, K. G., et al. (1995). "Cellular immortality: a late event in the progression of human squamous cell carcinoma of the head and neck associated with p53 alteration and a high frequency of allele loss." Mol Carcinog 13(4): 254-265.

Many human tumors contain variant cells that, unlike their normal counterparts, possess indefinite proliferative potential in vitro. However, little is known of the relevance of these immortal cells to human carcinomas in vivo. To investigate immortality in a human tumor system, we established cultures from different stages of head and neck squamous carcinoma (SCC-HN). All the neoplastic cultures were transformed because they showed very low cornification in surface or suspension culture and were partially or completely resistant to suspension-induced death. Immortal variants were not detected in premalignant erythroplakia cultures, but their frequency increased with tumor progression, indicating that immortality is a late event in carcinogenesis. Some late-stage carcinomas still produced senescent cultures, but, significantly, all recurrent tumors were immortal. Immortal but not senescent carcinoma cultures were associated with p53 dysfunction and a high frequency of allele loss, indicative of tumor suppressor gene inactivation. These results show that there are at least two classes of human SCC-HN that are phenotypically and genotypically distinct and that the pathological stage of a given tumor is not necessarily indicative of the kind of cells it contains.

Eissenberg, J. C. (2018). "Hungering for Immortality." Mo Med 115(1): 12-17.

Beyond avoiding risky behavior-smoking, substance abuse, obesity-and embracing healthy habits like exercise, a balanced diet, and non-obese body weight, are there things we each do today to significantly extend our lifespan? Caloric restriction is the only behavioral intervention consistently shown to extend both mean and maximal lifespan across a wide range of species. In most cases, the lifespan extension is accompanied by a marked delay in the onset of age-associated disease and infirmity.

Elgueta, R., et al. (2010). "The immortality of humoral immunity." Immunol Rev 236: 139-150.

Decades of high-titered antibody are sustained due to the persistence of memory B cells and long-lived plasma cells (PCs). The differentiation of each of these subsets is antigen- and T-cell driven and is dependent on signals acquired and integrated during the germinal center response. Inherent in the primary immune response must be the delivery of signals to B cells to create these populations, which have virtual immortality. Differences in biology and chemotactic behavior disperse memory B cells and long-lived PCs to a spectrum of anatomic sites. Each subset must rely on survival factors that can support their longevity. This review focuses on the generation of each of these subsets, their survival, and renewal, which must occur to sustain serological memory. In this context, we discuss the role of antigen, bystander inflammation, and cellular niches. The contribution of BAFF (B-cell activating factor belonging to the tumor necrosis factor family) and APRIL (a proliferation-inducing ligand) to the persistence of memory B cells and PCs are also detailed. Insights that have been provided over the past few years in the regulation of long-lived B-cell responses will have profound impact on vaccine development, the treatment of pre-sensitized patients for organ transplantation, and therapeutic interventions in both antibody- and T-cell-mediated autoimmunity.

Endo, S. and L. Hieber (1995). "Chromosome alterations that correlate with progression to immortality in Syrian hamster embryo cells transformed by gamma-irradiation." Int J Radiat Biol 67(2): 177-186.

Primary Syrian hamster embryo (SHE) cells can be transformed in vitro by gamma-irradiation or spontaneously and display morphological alterations in discrete colonies as the earliest recognizable transformants. These morphologically transformed colonies can progress to give rise to immortal cell lines. The purpose of the present study was to determine if specific chromosome changes occur that correlate with immortalization. In the non-irradiated culture, 18 transformed colonies were isolated, of which two became immortal. In the irradiated culture, six out of

18 transformed colonies isolated progress to immortalization. Seven out of eight immortalized cell lines exhibited either numerical and/or structural chromosome alterations. Of six radiation-induced immortal lines, four lines showed rearrangements in the long arms of chromosome 3 (3q +) and chromosome 6 (6q +) non-randomly. In all cases, both 3q + and 6q + were detected in the primary transformed colonies from which the immortal cell lines arose. Both 3q + and 6q + occurred always as heterozygotes in the primary-transformed colonies. 3q + and 6q + were never found in the non-irradiated culture, demonstrating that these chromosome changes were induced by irradiation. 3q + and 6q + may correlate with progression to immortality in SHE cells transformed by gamma-irradiation.

Endo, S., et al. (1990). "Nonrandom chromosome alterations that correlate with progression to immortality in rat tracheal epithelial cells transformed with N-methyl-N'-nitro-N-nitrosoguanidine." Cancer Res 50(3): 740-747.

Primary rat tracheal epithelial cells can be transformed in vitro by N-methyl-N'-nitro-N-nitrosoguanidine. The earliest recognizable morphological transformant is the enhanced growth variant (EGV), characterized by enhanced proliferative capacity. Transformed EGV colonies can progress to give rise to immortal cell lines. The purpose of this study was to determine if specific chromosome changes occur which correlate with immortalization. A total of 34 EGV colonies were isolated, of which five were able to progress in culture to become immortal (greater than or equal to 100 population doublings). Early passages of all five immortalized cultures exhibited additional copies of chromosomes 4, 7, and 11 as a common or recurrent abnormality. These numerical alterations were rarely observed in the primary EGV colonies from which the cell lines were derived, suggesting that these alterations occurred during progression. Structural alterations involving chromosome 1 (resulting in a net gain of 1q) and chromosome 3(3q) also occurred in four out of five immortalized cultures. In all cases, structural alterations involving 1q and/or 3q were detected in the primary EGV colonies from which the immortal cell lines arose. Comparison of the frequency of the structural and numerical alterations observed in the immortalized cultures with their frequency in the 29 EGV colonies which did not become immortal indicated that these changes correlated (P less than or equal to 0.005) with the ability to become immortal. These results suggest that structural alterations occur in primary EGV colonies which predispose cells to immortalization and that subsequent numerical changes occur during progression that correlate with acquisition of the immortal phenotype.

Engelhardt, M. and U. M. Martens (1998). "The implication of telomerase activity and telomere stability for replicative aging and cellular immortality (Review)." Oncol Rep 5(5): 1043-1052.

Telomerase and telomeres have been shown to be involved in the control of cell proliferation, the regulation of cell senescence and the unlimited proliferation capacity of malignant cells. Human telomeres are specialized chromosomal end structures composed of TTAGGG repeats. They function to protect chromosomes from degradation, fusion and recombination. Since the termini of linear molecules are replicated only in the 5'-3' direction by conventional DNA polymerases and require an RNA primer to initiate DNA synthesis, the removal of the RNA primer results in DNA loss with each cell division. To date, telomere shortening has been observed in most dividing somatic cells, eventually leading to cell senescence when critically short telomeres are reached. Telomerase has been identified as a ribonucleoprotein enzyme that can synthesize telomeric repeats onto chromosomes. Borderline telomerase activity has been detected in human primitive hematopoietic cells and in stimulated lymphocytes which increased with cytokine induced ex vivo expansion. However, in most other normal somatic cells, telomerase has not been detected, and consequently telomere shortening can be anticipated after a limited number of population doublings. In contrast, spontaneously immortalized tumor cell lines and the majority of malignant tumors demonstrate high telomerase activity, stable telomere length and unlimited proliferative potential. Mechanisms for telomerase and telomere length regulation are under extensive investigation. These have included the cloning of the RNA component and telomerase associated proteins, antisense experiments that have demonstrated progressive telomere length shortening in the absence of telomerase, and the identification of telomere binding proteins which may regulate telomerase by creating a negative feedback signal. This review aims to summarize important results in the rapidly moving field of telomeres and telomerase.

Erenpreisa, J. and M. S. Cragg (2013). "Three steps to the immortality of cancer cells: senescence, polyploidy and self-renewal." Cancer Cell Int 13(1): 92.

Metastatic cancer is rarely cured by current DNA damaging treatments, apparently due to the development of resistance. However, recent data indicates that tumour cells can elicit the opposing processes of senescence and stemness in response to these treatments, the biological significance and molecular regulation of which is currently poorly understood. Although cellular senescence is typically considered a terminal cell fate, it was recently shown to be reversible in a small population of polyploid cancer cells induced after DNA damage. Overcoming

genotoxic insults is associated with reversible polyploidy, which itself is associated with the induction of a stemness phenotype, thereby providing a framework linking these separate phenomena. In keeping with this suggestion, senescence and autophagy are clearly intimately involved in the emergence of self-renewal potential in the surviving cells that result from de-polyploidisation. Moreover, subsequent analysis indicates that senescence may paradoxically be actually required to rejuvenate cancer cells after genotoxic treatments. We propose that genotoxic resistance is thereby afforded through a programmed life-cycle-like process which intimately unites senescence, polyploidy and stemness.

Ertel, A., et al. (2012). "Is cancer a metabolic rebellion against host aging? In the quest for immortality, tumor cells try to save themselves by boosting mitochondrial metabolism." Cell Cycle 11(2): 253-263.

Aging drives large systemic reductions in oxidative mitochondrial function, shifting the entire body metabolically towards aerobic glycolysis, a.k.a, the Warburg effect. Aging is also one of the most significant risk factors for the development of human cancers, including breast tumors. How are these two findings connected? One simplistic idea is that cancer cells rebel against the aging process by increasing their capacity for oxidative mitochondrial metabolism (OXPHOS). Then, local and systemic aerobic glycolysis in the aging host would provide energy-rich mitochondrial fuels (such as L-lactate and ketones) to directly "fuel" tumor cell growth and metastasis. This would establish a type of parasite-host relationship or "two-compartment tumor metabolism", with glycolytic/oxidative metabolic-coupling. The cancer cells ("the seeds") would flourish in this nutrient-rich microenvironment ("the soil"), which has been fertilized by host aging. In this scenario, cancer cells are only trying to save themselves from the consequences of aging, by engineering a metabolic mutiny, through the amplification of mitochondrial metabolism. We discuss the recent findings of Drs. Ron DePinho (MD Anderson) and Craig Thomspson (Sloan-Kettering) that are also consistent with this new hypothesis, linking cancer progression with metabolic aging. Using data mining and bioinformatics approaches, we also provide key evidence of a role for PGC1a/NRF1 signaling in the pathogenesis of (1) two-compartment tumor metabolism, and (2) mitochondrial biogenesis in human breast cancer cells.

Florea, M. (2017). "Aging and immortality in unicellular species." Mech Ageing Dev 167: 5-15.

It has been historically thought that in conditions that permit growth, most unicellular species do not to age. This was particularly thought to be the case for symmetrically dividing species, as such species lack a clear distinction between the soma and the germline. Despite this, studies of the symmetrically dividing species Escherichia coli and Schizosaccharomyces pombe have recently started to challenge this notion. They indicate that E. coli and S. pombe do age, but only when subjected to environmental stress. If true, this suggests that aging may be widespread among microbial species in general, and that studying aging in microbes may inform other long-standing questions in aging. This review examines the recent evidence for and against replicative aging in symmetrically dividing unicellular organisms, the mechanisms that underlie aging, why aging evolved in these species, and how microbial aging fits into the context of other questions in aging.

Florian, V. and M. Mikulincer (1998). "Symbolic immortality and the management of the terror of death: the moderating role of attachment style." J Pers Soc Psychol 74(3): 725-734.

Three studies were designed to examine the contribution of R. J. Lifton's (1979) symbolic immortality construct to the management of the terror of death and to investigate whether attachment style may underlie this contribution. Using a sample of 420 Israeli students, Study 1 revealed an inverse correlation between self-reports of symbolic immortality and fear of personal death. This finding was validated in Study 2 (N = 120), which found that high symbolic immortality reduced the effects of a death salience manipulation on the level of punishment given to a social transgressor. Study 3 (N = 270) refined the association between symbolic immortality and fear of death. The inverse correlation found in Study 1 was revealed only among securely attached persons. The discussion emphasizes the interconnectedness between personality, symbolic immortality, and the management of the terror of death.

Fuller, M. T. and A. C. Spradling (2007). "Male and female Drosophila germline stem cells: two versions of immortality." Science 316(5823): 402-404.

Drosophila male and female germline stem cells (GSCs) are sustained by niches and regulatory pathways whose common principles serve as models for understanding mammalian stem cells. Despite striking cellular and genetic similarities that suggest a common evolutionary origin, however, male and female GSCs also display important differences. Comparing these two stem cells and their niches in detail is likely to reveal how a common heritage has been adapted to the differing requirements of male and female gamete production.

Furuhashi, H. and W. G. Kelly (2010). "The epigenetics of germ-line immortality: lessons from an elegant model system." Dev Growth Differ 52(6): 527-532.

Epigenetic mechanisms are thought to help regulate the unique transcription program that is established in germ cell development. During the

germline cycle of many organisms, the epigenome undergoes waves of extensive resetting events, while a part of epigenetic modification remains faithful to specific loci. Little is known about the mechanisms underlying these events, how loci are selected for, or avoid, reprogramming, or even why these events are required. In particular, although the significance of genomic imprinting phenomena involving DNA methylation in mammals is now well accepted, the role of histone modification as a transgenerational epigenetic mechanism has been the subject of debate. Such epigenetic mechanisms may help regulate transcription programs and/or the pluripotent status conferred on germ cells, and contribute to germ line continuity across generations. Recent studies provide new evidence for heritability of histone modifications through germ line cells and its potential effects on transcription regulation both in the soma and germ line of subsequent generations. Unraveling transgenerational epigenetic mechanisms involving highly conserved histone modifications in elegant model systems will accelerate the generation of new paradigms and inspire research in a wide variety of fields, including basic developmental studies and clinical stem cell research.

Gallagher, T. (2014). "The immortality of Ms Jones." Ann Fam Med 12(4): 373-374.

When I began my medical student clinical rotations, I quickly became overwhelmed by feelings of inadequacy. While the doctors around me conjured appropriate diagnoses and treatment approaches, I fumbled with the only tools I possessed: my time and a smile. It was only when I met the patient Ms Jones that I came to understand the potential impact of these simple tools. My encouragement became part of her recovery process. She gave me the confidence to construct this ability of comforting patients into a small platform of confidence from which I could safely venture to educate patients or suggest treatments to residents. It could be something that I could reliably fall back on in times of doubt and something I could pass along to other people I met.

Garbe, J., et al. (1999). "Viral oncogenes accelerate conversion to immortality of cultured conditionally immortal human mammary epithelial cells." Oncogene 18(13): 2169-2180.

Our recent studies on the process of immortalization of cultured human mammary epithelial cells (HMEC) have uncovered a previously undescribed, apparently epigenetic step, termed conversion. When first isolated, clonally derived HMEC lines of indefinite lifespan showed little or no telomerase activity or ability to maintain growth in the presence of TGFbeta. Cell populations whose mean terminal restriction fragment length had declined to <3 kb also exhibited slow heterogeneous growth, and contained many non-proliferative cells. With continued passage, these conditionally immortal cell populations very gradually converted to a fully immortal phenotype of good growth+/-TGFbeta, expression of high levels of telomerase activity, and stabilization of telomere length. We now show that exposure of the early passage conditionally immortal 184A1 HMEC line to the viral oncogenes human papillomavirus type 16 (HPV16)-E6, -E7, or SV40T, results in either immediate (E6) or rapid (E7; SV40T) conversion of these telomerase negative, TGFbeta sensitive conditionally immortal cells to the fully immortal phenotype. Unlike conditional immortal 184A1, the HPV16-E7 and SV40T exposed cells were able to maintain growth in TGFbeta prior to expression of high levels of telomerase activity. A mutated HPV16-E6 oncogene, unable to inactivate p53, was still capable of rapidly converting conditional immortal 184A1. Our studies provide further evidence that the transforming potential of these viral oncogenes may involve activities beyond their inactivation of p53 and pRB functions. These additional activities may greatly accelerate a step in HMEC immortal transformation, conversion, that would be rate-limiting in the absence of viral oncogene exposure.

Gentile, S. (2016). "hERG1 potassium channel in cancer cells: a tool to reprogram immortality." Eur Biophys J 45(7): 649-655.

It has been well established that changes in ion fluxes across cellular membranes as a function of time is fundamental in maintaining cellular homeostasis of every living cell. Consequently, dysregulation of ion channels activity is a critical event in pathological conditions of several tissues, including cancer. Nevertheless, the role of ion channels in cancer biology is still not well understood and very little is known about the possible therapeutic opportunities offered by the use of the vast collection of drugs that target ion channels. In this review, we focus on the recent advances in understanding the role of the voltage-gated hERG1 potassium channel in cancer and on the effects of pharmacologic manipulation of the hERG1 in cancer cells aiming to provide insights into the biochemical signaling and cellular processes that are altered by using these drugs.

Gire, V. (2005). "[Senescence: a telomeric limit to immortality or a cellular response to physiologic stresses?]." Med Sci (Paris) 21(5): 491-497.

Cells entering a state of senescence undergo a irreversible cell cycle arrest, associated by a set of functional and morphological changes. Senescence occurs following telomeres shortening (replicative senescence) or exposure to other acute or chronic physiologic stress signals (a phenomenon termed stasis: stress or aberrant signaling-induced senescence). In this review, I discuss the pathways of cellular senescence,

the mechanisms involved and the role that these pathways have in regulating the initiation and progression of cancer. Telomere-initiated senescence or loss of telomere function trigger focal recruitement of protein sensors of the DNA double-strand breaks leading to the activation of the DNA damage checkpoint responses and the tumour suppressor gene product, p53, which in turn induces the cell-cycle inhibitor, p21(WAF1). Loss of p53 and pRb function allows continued cell division despite increasing telomere dysfunction and eventually entry into telomere crisis. Immortalisation is an essential prerequisite for the formation of a tumour cell. Therefore, a developing tumour cell must circumvent at least two proliferative barriers--cellular senescence and crisis--to achieve neoplastic transformation. These barriers are regulated by telomere shortening and by the p16(INK4a)/Rb and p53 tumour suppressor pathways. Elucidation of the genes and emerging knowledge about the regulatory mechanisms that lead to senescence and determine the pattern of gene expression in senescent cells may lead to more effective treatments for cancer.

Glenn, J. (1995). "The child is father of the man. Wordsworth's Ode: Intimations of immortality and his secret sharers." Psychoanal Study Child 50: 383-397.

William Wordsworth's "Ode: Intimations of Immortality" is manifestly about both the poet's loss of inspirational perceptive powers and emotional intensity with age, and the compensations of maturity. It also refers to the poet's fear that he might lose his "secret sharers," real or fantasied, consciously or unconsciously conceived parent substitutes for whom and with whom one creates. Wordsworth anticipated that with his upcoming marriage he would lose his sister Dorothy and his close friend and collaborator Samuel Taylor Coleridge, who played important roles in his creativity. Optimism and relief replaced sadness when he realized that he was not deprived of his sharers. The concepts of "secret sharers" and "collective alternates" for whom one creates are intimately related.

Goding, C. R. (2011). "Commentary. A picture of Mitf in melanoma immortality." Oncogene 30(20): 2304-2306.

The Mitf gene has a key role in melanocytes and melanoma by regulating cell cycle progression, survival and differentiation. Two papers in this issue of Oncogene (Cheli et al., 2011; Strub et al., 2011) reveal that low-Mitf cells can initiate tumors with high efficiency, and that Mitf blocks senescence by regulating genes implicated in S-phase progression and mitosis.

Goldwert, M. (1985). "Otto Rank and man's urge to immortality." J Hist Behav Sci 21(2): 169-177.

Otto Rank, one of Sigmund Freud's original followers, posited the existence of an "urge to immortality" as man's deepest drive. In his Psychology and the Soul, Rank traced the desire for immortality through four historical eras, with particular emphasis on the creativity of the hero and the artist. By the end of his life, Rank had not only repudiated orthodox psychoanalysis and developed then abandoned a psychology of the will, he had moved "beyond psychology" to a religious view of history and the nature of man.

Gomez, J. M. (2010). "Aging in bacteria, immortality or not-a critical review." Curr Aging Sci 3(3): 198-218.

Bacteria were traditionally thought to have a symmetrical binary fission without a clear distinction between soma and germ-line, being thus considered as immortal biological entities. Yet it has been recently described that bacteria also undergo replicative aging (RA). That is, they exhibit finite replicative abilities under good conditions to growth. The apparently initial indistinguishability of sibling cells after cytokinesis is broken. After division, the daughter cell that inherits the "old" pole present in the "mother cell" progressively exhibits a decline in its proliferative capacity with increasing cell pole age. This is a clear hallmark and phenotypic manifestation of a bona fide RA phenomenon in toto. While the exact molecular mechanism(s) underlying to this lost of replicative potential are not yet fully understood, the "old pole cell" is considered as an aging parent that in a repeatedly manner is able to produce rejuvenated offspring which inherit a resetting of the biological clock. On the order hand, bacteria exhibit in addition to this "mandatory" RA the dubbed conditional senescence (CS). CS is defined as a decline in cellular viability observed in arrested-growing bacteria populations, a phenomenon apparently not related to RA under growing active conditions. To understand bacterial aging, it is necessary to put it within the sociality-multicellularity framework. This is a new conceptual paradigm that expresses the natural reality of the bacterial world. From this more ecological perspective these bacterial aging phenomena probably should represent an insurance/bethedging anticipative survival strategy. This is underpinned in a self-generation of an appropriate level of populational phenotypic diversity. That is, bacterial aging could be considered a communitarian adaptive response to cope with different environmental stresses and threats. I have highlighted the necessity to construct an integrative conceptual framework to achieve a unified view of bacteria aging to answer this fundamental question: what are the reasons of bacterial aging?

Gordon, K., et al. (2014). "Immortality, but not oncogenic transformation, of primary human cells leads to epigenetic reprogramming of DNA methylation and gene expression." Nucleic Acids Res

42(6): 3529-3541.

Tumourigenic transformation of normal cells into cancer typically involves several steps resulting in acquisition of unlimited growth potential, evasion of apoptosis and non-responsiveness to growth inhibitory signals. Both genetic and epigenetic changes can contribute to cancer development and progression. Given the vast genetic heterogeneity of human cancers and difficulty to monitor cancer-initiating events in vivo, the precise relationship between acquisition of genetic mutations and the temporal progression of epigenetic alterations in transformed cells is largely unclear. Here, we use an in vitro model system to investigate the contribution of cellular immortality and oncogenic transformation of primary human cells to epigenetic reprogramming of DNA methylation and gene expression. Our data demonstrate that extension of replicative life span of the cells is sufficient to induce accumulation of DNA methylation at gene promoters and large-scale changes in gene expression in a time-dependent manner. In contrast, continuous expression of cooperating oncogenes in immortalized cells, although essential for anchorage-independent growth and evasion of apoptosis, does not affect de novo DNA methylation at promoters and induces subtle expression changes. Taken together, these observations imply that cellular immortality promotes epigenetic adaptation to highly proliferative state, whereas transforming oncogenes confer additional properties to transformed human cells.

Graur, D., et al. (2013). "On the immortality of television sets: "function" in the human genome according to the evolution-free gospel of ENCODE." Genome Biol Evol 5(3): 578-590.

A recent slew of ENCyclopedia Of DNA Elements (ENCODE) Consortium publications, specifically the article signed by all Consortium members, put forward the idea that more than 80% of the human genome is functional. This claim flies in the face of current estimates according to which the fraction of the genome that is evolutionarily conserved through purifying selection is less than 10%. Thus, according to the ENCODE Consortium, a biological function can be maintained indefinitely without selection, which implies that at least 80 - 10 = 70% of the genome is perfectly invulnerable to deleterious mutations, either because no mutation can ever occur in these "functional" regions or because no mutation in these regions can ever be deleterious. This absurd conclusion was reached through various means, chiefly by employing the seldom used "causal role" definition of biological function and then applying it inconsistently to different biochemical properties, by committing a logical fallacy known as "affirming the consequent," by failing to appreciate the crucial difference between "junk DNA" and "garbage DNA," by using analytical methods that yield biased errors and inflate estimates of functionality, by favoring statistical sensitivity over specificity, and by emphasizing statistical significance rather than the magnitude of the effect. Here, we detail the many logical and methodological transgressions involved in assigning functionality to almost every nucleotide in the human genome. The ENCODE results were predicted by one of its authors to necessitate the rewriting of textbooks. We agree, many textbooks dealing with marketing, mass-media hype, and public relations may well have to be rewritten.

Hayflick, L. (1997). "Mortality and immortality at the cellular level. A review." Biochemistry (Mosc) 62(11): 1180-1190.

A brief history of cell culture as it pertains to aging research had its origins with the thoughts of Weismann and the work of Carrel. Until the early 1960's it was believed that normal cells had an unlimited capacity to replicate. Consequently, aging was thought to have little to do with intracellular events. In the early 1960's we overthrew this dogma after finding that normal cells do have a finite replicative capacity. We interpreted this phenomenon to be aging at the cellular level. In subsequent years the objective was to identify the putative cell division counting mechanism that had been postulated to exist. Efforts to achieve this goal have had a remarkable degree of success only in the last few years with the discovery of the shortening of telomeres at each round of DNA replication that occurs in normal cells both in vivo and in vitro. Immortal abnormal cell populations overcome telomere shortening by activating an enzyme, telomerase, that catalyzes the synthesis of the TTAGGG sequences that compose mammalian telomeres, thus maintaining their length constant. Telomere shortening in normal cells is not a chronometer because time is not measured but rounds of DNA replication are measured. I propose the term replicometer for the device that measures the loss of telomeric sequences in normal cells because the action is that of a meter, and it is counting DNA replications. Telomere shortening and the finite lifetime of normal cells is more likely to represent longevity determination than it is aging. The hundreds of biological changes that herald the loss of replicative capacity in normal cells are more likely age changes.

Hayflick, L. (1998). "A brief history of the mortality and immortality of cultured cells." Keio J Med 47(3): 174-182.

During the first half of this century it was believed that because cultured normal cells were immortal, aging must be caused by extracellular events. Thirty-five years ago we overthrough this dogma when we discovered that normal cells do have a limited capacity to divide and that aging occurs intracellularly.

We also observed that only cancer cells are immortal. Normal cells are mortal because telomeres shorten at each division. Immortal cancer cells express the enzyme telomerase that prevents shortening. Recently, it was discovered that the telomerase gene when inserted into normal cells immortalizes them. There appears to be a relationship between these findings and aging, longevity determination and cancer. After performing the miracles that take us from conception to birth, and then to sexual maturation and adulthood, natural selection was unable to favor the development of a more elementary mechanism that would simply maintain those earlier miracles forever. This failure is called aging. Because few feral animals age, evolution could not have favored animals exhibiting age changes. Natural selection favors animals that are most likely to become reproductively successful by developing greater survival skills and reserve capacity in vital systems to better survive predation, disease, accidents and environmental extremes. Natural selection diminishes after sexual maturation because the species will not benefit from members favored for greater development of physiological reserve. A species betters its chances of survival by investing its resources and energy in increasing opportunities for reproductive success rather than on post-reproductive longevity. The level of physiological reserve remaining after reproductive maturity determines potential longevity and evolves incidental to the selection process that acts on earlier developmental events. Physiological reserve does not renew at the same rate that it incurs losses because molecular disorder increases. These age changes increase vulnerability to predation, accidents or disease.

Hayflick, L. (1999). "[A brief overview of the discovery of cell mortality and immortality and of its influence on concepts about aging and cancer]." Pathol Biol (Paris) 47(10): 1094-1104.

After having accomplished the miraculous performance that led us from conception to birth, then to sexual maturity and adulthood, natural selection failed to develop a more elementary mechanism capable of simply maintaining the results of this process forever. This failure is aging. Because few animals age in the wild, evolution could not give an advantage to animals with modifications due to aging. Natural selection benefits those animals that have the highest likelihood of effectively perpetuating their species because their vital systems have the larger reserve capacity they need to resist and survive predators, disease, injury, and extreme environmental conditions. Natural selection decreases after sexual maturity has been reached because at that stage the species would not derive additional advantages from individuals with larger physiological reserves. A species increases its likelihood of survival by investing its resources and energy into increasing its opportunities for fruitful reproduction rather than into prolonging its postreproductive life span. Most animals are mortal and undergo aging because investment of resources into keeping the body eternally youthful does not promote species survival as much as their investment into strategies that make reproduction more successful.

Hayflick, L. (2000). "The illusion of cell immortality." Br J Cancer 83(7): 841-846.

Normal cultured cell populations are mortal but cells that are immortal are abnormal and most have properties of cancer cells. Nevertheless, this distinction becomes blurred because the terms 'mortality' and 'immortality' are subject to enormous variations in understanding. Forty years ago we showed that cell mortality and immortality are inextricably linked to longevity determination, ageing and cancer. We suggested that a counting mechanism existed in normal cells and that has now been identified as telomere attrition. This replicometer, in combination with the discovery of the enzyme telomerase, has gone very far in explaining why most normal somatic cells have a finite capacity to replicate both in vivo and in vitro and how immortal cancer cells circumvent this inevitability. It is suggested that telomere attrition may be better understood as a direct measure of longevity determination and to only have an indirect association with age changes.

Hazzard, W. R. and W. H. Ettinger, Jr. (1995). "Aging and Atherosclerosis: Changing Considerations in Cardiovascular Disease Prevention as the Barrier to Immortality is Approached in Old Age." Am J Geriatr Cardiol 4(4): 16-36.

Of all the risk factors to cardiovascular disease (CVD), age is the most powerful: CVD incidence and prevalence rise progressively at all ages beyond young adulthood. This reflects the central role of time, and hence duration, in the atherogenic process. It also reflects age-related changes in physiology - notably alterations in body mass and composition favoring increased adiposity and in sex hormone secretion (combining adverse effects of androgens on lipoprotein lipid levels in males, lowering HDL, and of the decline in estrogens in postmenopausal females, raising LDL). The interactions among the passage of time, these physiological changes and perhaps aging per se, and pathological forces such as cigarette smoking, hypertension, and genetically determined dyslipoproteinemia conspire to accelerate the rate of atherogenesis. Thus clinical atherosclerosis and its complications rise exponentially with increasing age in the population at large. However, the relationship between dyslipoproteinemia and CVD risk in the individual patient actually declines with advancing age. This apparent paradox reflects confounding introduced

by the advent of disease processes that cause wasting and inflammation such as cancer, infection, diabetes, trauma, and even CVD that actually lower lipid levels, frequently to the level of hypocholesterolemia. Thus, while with age the population-attributable risk of hypercholesterolemia (and/or low HDL) rises, the cholesterol-attributable risk in the individual falls. As a result the prescription of lipid-lowering therapy in elderly patients requires exquisite individualization: patients most likely to benefit are those with existing CVD (i.e., in secondary prevention) who nevertheless enjoy robust health and are highly motivated to comply with demanding regimens of diet and exercise plus drugs where needed to reach target LDL levels (less than 100 mg/dl). At the other extreme are those least likely to benefit: patients who are frail and failing from CVD or other wasting diseases of old age that present a more immediate threat to survival.

Heber-Katz, E., et al. (2006). "Conjecture: Can continuous regeneration lead to immortality? Studies in the MRL mouse." Rejuvenation Res 9(1): 3-9.

A particular mouse strain, the MRL mouse, has been shown to have unique healing properties that show normal replacement of tissue without scarring. The serendipitous discovery that the MRL mouse has a profound capacity for regeneration in some ways rivaling the classic newt and axolotl species raises the possibility that humans, too, may have an innate regenerative ability. We propose this mouse as a model for continuous regeneration with possible life-extending properties. We will use the classical "immortal" organism, the hydra, for comparison and examine those key phenotypes that contribute to their immortality as they are expressed in the MRL mouse versus control mouse strains. The phenotypes to be examined include the rate of proliferation and the rate of cell death, which leads to a continual turnover in cells without an increase in mass.

Holland, A. M. and E. G. Stanley (2009). "Stems cells and the price of immortality." Stem Cell Res 2(1): 26-28.

Holme, P. (2015). "Shadows of the susceptible-infectious-susceptible immortality transition in small networks." Phys Rev E Stat Nonlin Soft Matter Phys 92(1): 012804.

Much of the research on the behavior of the SIS model on networks has concerned the infinite size limit; in particular the phase transition between a state where outbreaks can reach a finite fraction of the population, and a state where only a finite number would be infected. For finite networks, there is also a dynamic transition-the immortality transition-when the per-contact transmission probability lambda reaches 1. If lambda<1, the probability that an outbreak will survive by an observation time t tends to zero as t-->infinity; if lambda=1, this probability is 1. We show that treating lambda=1 as a critical point predicts the lambda dependence of the survival probability also for more moderate lambda values. The exponent, however, depends on the underlying network. This fact could, by measuring how a vertex's deletion changes the exponent, be used to evaluate the role of a vertex in the outbreak. Our work also confirms an extremely clear separation between the early die-off (from the outbreak failing to take hold in the population) and the later extinctions (corresponding to rare stochastic events of several consecutive transmission events failing to occur).

Ishii, Y., et al. (1999). "Telomerase activity in hybrids between telomerase-negative and telomerase-positive immortal human cells is repressed in the different complementation groups but not in the same complementation group of immortality." Mech Ageing Dev 110(3): 175-193.

The expression of telomerase is essential for cells to be immortalized, and most immortal cell lines possessed telomerase activity. Using the cell fusion technique, it has been shown that mortal and telomerase-negative phenotypes of normal cells are dominant over immortal and telomerase-positive phenotypes, suggesting that the normal cells possessed dominant repressor-type activity for telomerase expression. Several telomerase-negative immortal human cell lines were reported, in which telomerase-independent mechanisms was supposed to maintain telomere length. We aimed at seeing whether the telomerase-negative phenotype of these immortal cells is dominant over telomerase-positive phenotype of other immortal cells in correlation with cellular mortality. Results showed that, when telomerase-positive and -negative immortal parental cell lines belonging to the different complementation groups were fused, telomerase-negative mortal hybrid clones arose, i.e. telomerase-negative phenotype was dominant as well as mortal phenotype. However, when immortal hybrid cells arose from telomerase-positive and -negative immortal parents belonging to either the same or different complementation groups, they were all telomerase-positive, i.e. telomerase-negative phenotype appeared to be recessive. Telomerase-negative immortal hybrid was never established from any combinations between telomerase-negative and -positive immortal parental cells.

Jacquemin-Sablon, H., et al. (1990). "Transfer of immortality by transfection of genomic DNA from SV40 established cell lines into rat embryo fibroblasts." Biol Cell 68(3): 227-230.

The cellular immortalization activity of cloned genes can be identified either in a colony-forming assa of transfected primary rat embryo fibroblasts or in a co-operation assay together with ras. However the demonstration of immortalization activities carried by

cellular genes has not been reported. Here we establish that SV40 early genes integrated in genomic DNAs can be stably transferred into rat embryo fibroblasts and selected via their immortalization activity. Attempts to extend this assay to the identification of dominant genes putatively involved in the immortality of several other immortal post-crisis or tumor cells have been unsuccessful suggesting that the immortal phenotype can be brought about through different pathways.

Janknecht, R. (2004). "On the road to immortality: hTERT upregulation in cancer cells." FEBS Lett 564(1-2): 9-13.

Telomere attrition limits the replicative potential of most somatic cells. In contrast, tumor cells acquire immortality by continuous telomere maintenance which is predominantly due to the transcriptional upregulation of the limiting component of telomerase, hTERT (human telomerase reverse transcriptase). Recent findings have provided mechanistic insight into how oncogenic activation as well as derepression, often due to the inactivation of tumor suppressors, stimulate the hTERT promoter. Knowledge gained from the study of hTERT transcriptional regulation may prove instrumental in the development of cancer therapies directed at the suppression of telomerase activity in tumor cells.

Janot, F. (2000). "[Gold amulets of Ra: a step towards immortality]." Vesalius 6(1): 32-37.

In Ancient Egypt, the priest-embalmer laid the gold on the whole of the king's body. For simple citizens, he more modestly applied fine leaves or amulets of golden wax for certain parts. Possessing the same magical powers as gold, they participated in the complete preservation.

Johnson, S. B., et al. (2015). "Time to Nadir PSA: Of Popes and PSA--The Immortality Bias." Am J Clin Oncol 38(5): 465-471.

OBJECTIVES: The objective of the study was to investigate prostate-specific antigen (PSA) nadir (nPSA) and time to nPSA (TnPSA) as prognostic variables for outcomes after definitive high-dose (>75 Gy) external beam radiation therapy (RT) without androgen deprivation therapy while correcting for immortal-time bias. METHODS: nPSA and TnPSA were available for 410 patients. nPSA and TnPSA's impact on freedom from biochemical failure, freedom from metastasis, and prostate cancer-specific survival was assessed on univariate and multivariate analysis using Kaplan-Meier and Cox proportional hazards regression. Outcomes were also evaluated relative to the time since achieving nPSA and not relative to the time of RT, given the intrinsic time bias in TnPSA. RESULTS: Median nPSA was 0.7 ng/mL (interquartile range: 0.4 to 1.1), with a median TnPSA of 25.0 months (IQR: 15.0 to 40.0). On univariate analysis both nPSA and TnPSA were predictive of all endpoints: freedom from biochemical failure, freedom from metastasis, and prostate cancer-specific survival, as categorical (all P<0.0001) and continuous (all P<0.01) variables. However, after adjusting for immortal-time bias the benefit of long TnPSA was mostly lost. On Cox proportional hazards, a TnPSA<12 months did have worse prognosis for biochemical failure and distant metastasis as compared with longer TnPSA, but for those who achieved nadir >12 months from the time of RT the TnPSA was no longer prognostic. CONCLUSIONS: For dose-escalated RT a lower nPSA is prognostic, but the benefit of a long TnPSA is largely an immortal-time bias and that a longer TnPSA is not in and of itself a significant favorable factor except as compared with those with the shortest TnPSA of <12 months.

Johnson, T. E. (2005). "Genes, phenes, and dreams of immortality: the 2003 Kleemeier Award lecture." J Gerontol A Biol Sci Med Sci 60(6): 680-687.

The 2002 Kleemeier Award from the Gerontological Society of America was awarded to Thomas E. Johnson, PhD, of the University of Colorado at Boulder. Dr. Johnson was the pioneer who first applied genetic analyses to the study of the aging processes in Caenorhabditis elegans and who introduced the nematode as an aging model. Longer life span was chosen as a surrogate marker for slowed aging. Here Dr. Johnson describes his role(s) in the isolation of age-1, the first longevity mutant, which can more than double the life span and which slows the rate of aging more than twofold. He also reviews research suggesting conservation of function and applicability to intervention by pharmacological targeting of the Age-1 pathway. Current work by biotechnology companies targets this and other basic discoveries in an attempt to postpone human aging.

Jonak, Z. L., et al. (1992). "Manipulation of human B cells to confer immortality." Hum Antibodies Hybridomas 3(4): 177-185.

Electroporation was used to deliver genomic DNA from a lymphoid tumor to activated/stimulated human peripheral blood lymphocytes to create immortalized lymphoid cell lines. Activation of the recipient lymphocytes was essential for efficient immortalization. A panel of human B cell transfectant clones, each phenotypically representing specific stages of differentiation, resulted from the transfection. Monoclonal antibody production was measured, and the level produced depended on the phenotype of the cells, with the more mature B cell transfectants secreting up to 10 micrograms/mL of immunoglobulin. The transfectants were stable with respect to their morphological appearance, growth rate, and antibody production. Chromosome analysis indicated that the transfectants displayed a normal karyotype, devoid of abnormalities. We have shown that electroporation is

an effective method of immortalizing human lymphocytes at different stages of differentiation. The transfectants provide a panel of cells that can readily be studied with respect to their phenotypic/karyotypic stability, regulation, and production of immunoglobulin, lymphokines, and growth factors. These data demonstrate the feasibility of generating immortalized human B cells to provide an important resource for the study of B cell differentiation and immortalization.

Jones, D. L. (2007). "Aging and the germ line: where mortality and immortality meet." Stem Cell Rev 3(3): 192-200.

Germ cells are highly specialized cells that form gametes, and they are the only cells within an organism that contribute genes to offspring. Germline stem cells (GSCs) sustain gamete production, both oogenesis (egg production) and spermatogenesis (sperm production), in many organisms. Since the genetic information contained within germ cells is passed from generation to generation, the germ line is often referred to as immortal. Therefore, it is possible that germ cells possess unique strategies to protect and transmit the genetic information contained within them indefinitely. However, aging often leads to a dramatic decrease in gamete production and fecundity. In addition, single gene mutations affecting longevity often have a converse effect on reproduction. Recent studies examining age-related changes in GSC number and activity, as well as changes to the stem cell microenvironment, provide insights into the mechanisms underlying the observed reduction in gametogenesis over the lifetime of an organism.

Kartsev, V. M. (2014). "Phenoptosis in arthropods and immortality of social insects." Biochemistry (Mosc) 79(10): 1032-1048.

In general, there are no drastic differences in phenoptosis patterns in plant and animal organisms. However, there are some specific features characteristic for insects and other arthropods: 1) their development includes metamorphosis with different biochemical laws at consecutive developmental stages; 2) arthropods can reduce or stop development and aging when in a state of diapause or temporal cold immobility; 3) their life cycle often correlates with seasonal changes of surroundings; 4) polymorphism is widespread - conspecifics differ by their lifespans and phenoptosis features; 5) lifespan-related sexual dimorphism is common; 6) significant situational plasticity of life cycle organization is an important feature; for example, the German wasp (Paravespula germanica) is obligatorily univoltine in the temperate zone, while in tropical regions its lifespan increases and leads to repeated reproduction; 7) life cycles of closely related species may differ significantly, for example, in contrast to German wasp, some tropical hornets (Vespa) have only one reproduction period. Surprisingly, many insect species have been shown to be subjected to gradual aging and phenoptosis, like the highest mammals. However, queens of social insects and some long-lived arachnids can apparently be considered non-aging organisms. In some species, lifespan is limited to one season, while others live much longer or shorter. Cases of one-time reproduction are rather rare. Aphagia is common in insects (over 10,000 species). Cannibalism is an important mortality factor in insects as well as in spiders. In social insects, which exist only in colonies (families), the lifetime of a colony can be virtually unlimited. However, in case of some species the developmental cycle and death of a colony after its completion are predetermined. Most likely, natural selection in insects does not lengthen individual lifespan, but favors increase in reproduction efficiency based on fast succession of generations leading to increased evolvability.

Kato, T., et al. (2007). "Activation of Holliday junction recognizing protein involved in the chromosomal stability and immortality of cancer cells." Cancer Res 67(18): 8544-8553.

We identified a novel gene HJURP (Holliday junction-recognizing protein) whose activation seemed to play a pivotal role in the immortality of cancer cells. HJURP was considered a possible downstream target for ataxia telangiectasia mutated signaling, and its expression was increased by DNA double-strand breaks (DSB). HJURP was involved in the homologous recombination pathway in the DSB repair process through interaction with hMSH5 and NBS1, which is a part of the MRN protein complex. HJURP formed nuclear foci in cells at S phase and those subjected to DNA damage. In vitro assays implied that HJURP bound directly to the Holliday junction and rDNA arrays. Treatment of cancer cells with small interfering RNA (siRNA) against HJURP caused abnormal chromosomal fusions and led to genomic instability and senescence. In addition, HJURP overexpression was observed in a majority of lung cancers and was associated with poor prognosis as well. We suggest that HJURP is an indispensable factor for chromosomal stability in immortalized cancer cells and is a potential novel therapeutic target for the development of anticancer drugs.

Katz, D. J., et al. (2009). "A C. elegans LSD1 demethylase contributes to germline immortality by reprogramming epigenetic memory." Cell 137(2): 308-320.

Epigenetic information undergoes extensive reprogramming in the germline between generations. This reprogramming may be essential to establish a developmental ground state in the zygote. We show that mutants in spr-5, the Caenorhabditis elegans ortholog of the H3K4me2 demethylase LSD1/KDM1, exhibit progressive sterility over many generations.

This sterility correlates with the misregulation of spermatogenesis-expressed genes and transgenerational accumulation of the histone modification dimethylation of histone H3 on lysine 4 (H3K4me2). This suggests that H3K4me2 can serve as a stable epigenetic memory, and that erasure of H3K4me2 by LSD/KDM1 in the germline prevents the inappropriate transmission of this epigenetic memory from one generation to the next. Thus, our results provide direct mechanistic insights into the processes that are required for epigenetic reprogramming between generations.

Keith, W. N. (2004). "From stem cells to cancer: balancing immortality and neoplasia." Oncogene 23(29): 5092-5094.

In this issue of Oncogene, Serakinci et al show that adult stem cells can be targets for neoplastic transformation. After transducing human adult mesenchymal stem cells (hMSC) with the telomerase hTERT gene, and growing them for many population doublings in culture, Serakinci et al observed that the transduced cells developed characteristics consistent with transformation including loss of contact inhibition, anchorage independence and tumour formation in mice. Underlying these changes were alterations to genes involved in cell cycle regulation and senescence as well as oncogene activation. The importance of these observations is twofold. Firstly, showing that stem cells can become tumours raises a note of caution for stem cell therapeutics. Secondly, the findings lend support to the stem cell hypothesis of cancer development, and provide an experimental system in which the tantalizing hint of new diagnostic, prognostic, and therapeutic opportunities offered by this concept can be explored further.

Keith, W. N., et al. (2004). "Drug insight: Cancer cell immortality-telomerase as a target for novel cancer gene therapies." Nat Clin Pract Oncol 1(2): 88-96.

Rapid advances in our understanding of the molecular basis of cancer development and progression over the past three decades have led to the design of new potential cancer therapies. High throughput target validation and expression studies are expected to yield a powerful arsenal of new cancer treatments, but untangling the complex pathways underlying the major cancer phenotypes remains a significant challenge. A considerable body of evidence in recent years implicates deregulated expression of a single multi-component enzyme, telomerase, as a causative factor at the heart of immortalization in the vast majority of human tumors. This review highlights the potential of telomerase as a target for novel cancer therapies. The potential of exploiting the selectivity of the telomerase family of genes within cancer cells to develop gene therapy strategies is discussed, and the progress towards translating these novel therapeutics from the laboratory to the clinic is reviewed.

Kelland, L. R. (2005). "Overcoming the immortality of tumour cells by telomere and telomerase based cancer therapeutics--current status and future prospects." Eur J Cancer 41(7): 971-979.

A key property of malignant tumours is their immortality or limitless replicative potential. Cell replication is associated with the maintenance of telomeres and in the great majority of cases, through the reactivation of the reverse transcriptase telomerase. Targeting the telomere/telomerase machinery offers a novel and potentially broad-spectrum anticancer therapeutic strategy since telomerase is constitutively overexpressed in the vast majority of human cancers. Telomeres are also critically short in most tumours compared to normal tissues. Strategies that exploit these differences include the direct targeting of components of telomerase: the protein component hTERT or RNA component hTR. Examples of such agents include the small molecule hTERT inhibitor BIBR1532 and GRN163L, a thio-phosphoramidate oligonucleotide targeting the template region of hTR as a "template antagonist". Anti-tumour effects have been observed in both cell lines and, especially for GRN163L, in xenografted human tumours in mice. Effects, however, are largely dependent upon initial telomere length, which can result in a substantial lag before antitumour activity is observed in tumours possessing relatively long telomeres. An alternative approach is to target the telomere itself (Telomere Targeting Agents, TTAs). Several classes of small molecules have been described that induce the G-rich single-stranded overhang of telomeric DNA to fold into 4-stranded G-quadruplex structures. Such folding is incompatible with telomerase function and may induce rapid telomere uncapping. These molecules have shown potent telomerase inhibition in nanomolar concentrations in vitro and the rapid induction of senescence in cancer cells. The trisubstituted acridine based TTA, BRACO19, has demonstrated single agent activity against human tumour xenografts with anti-tumour effects apparent from only 7 days of treatment. In the near future, it is expected that lead examples from both the direct telomerase targeted agents (e.g., GRN163L) and from the distinct class of those targeting telomeres (e.g., AS1410 based on BRACO19) will enter Phase I clinical trial where clinical benefit from this class of novel drugs will be determined.

Krupp, G., et al. (2000). "Telomerase, immortality and cancer." Biotechnol Annu Rev 6: 103-140.

Replication of eukaryotic linear chromosomes is incomplete and leaves terminal gaps. The evolutionary widely distributed solution to this "end replication" is twofold: chromosome ends are capped with telomeres, bearing multiple copies of redundant telomeric sequences, and the telomerase enzyme can add (lost) telomeric repeats. Telomerase in humans, as

in all mammals, is ubiquitous in all embryonic tissues. In adults, telomerase remains active in germs cells, and, although down-regulated in most somatic tissues, telomerase is active in regenerative tissues and notably, in tumor cells. Telomerase activity is linked to cellular proliferation, and its activation seems to be a mandatory step in carcinogenesis. In contrast to mammals, indeterminately growing multicellular organisms, like fish and crustaceae, maintain unlimited growth potential or 'immortality' in all somatic tissues throughout their entire life. Also this cell immortalization is brought about by maintaining telomerase expression. Disease prognosis for human tumors includes evaluation of cell proliferation, based on the detection of proliferation markers with monoclonal antibodies. The significance of the classical marker Ki-67, and of a novel marker repp-86 are compared with semiquantitative telomerase assays. For tumor therapy, telomerase inhibitors are attractive tools. Results with telomerase knock-out mice have revealed promise, but also risk of this approach. On the other side, telomerase stimulation is attractive for expanding the potential of cellular proliferation in vitro, with possible applications for transplantation of in vitro expanded human cells, for immortalizing primary human cells as improved tissue models, and for the isolation of otherwise intractable products, like genuine human monoclonal antibodies.

Kyriazis, M. (2014). "Reversal of informational entropy and the acquisition of germ-like immortality by somatic cells." Curr Aging Sci 7(1): 9-16.

We live within an increasingly technological, information-laden environment for the first time in human evolution. This subjects us (and will continue to subject us in an accelerating fashion) to an unremitting exposure to 'meaningful information that requires action'. Directly dependent upon this new environment are novel evolutionary pressures, which can modify existing resource allocation mechanisms and may eventually favour the survival of somatic cells (particularly neurons) at the expense of germ line cells. In this theoretical paper I argue that persistent, structured information-sharing in both virtual and real domains, leads to increased biological complexity and functionality, which reflects upon human survival characteristics. Certain biological immortalisation mechanisms currently employed by germ cells may thus need to be downgraded in order to enable somatic cells to manage these new energy demands placed by our modern environment. Relevant concepts from a variety of disciplines such as the evolution of complex adaptive systems, information theory, digital hyper-connectivity, and cell immortalisation will be reviewed. Using logical, though sometimes speculative arguments, I will attempt to describe a new biology. A biology not driven by sex and reproduction but by information and somatic longevity.

Lepperdinger, G. (2009). "Open-ended question: is immortality exclusively inherent to the germline?--A mini-review." Gerontology 55(1): 114-117.

All somatic cells are subject to aging. Germline links generations, and thus, pluripotent germ cells are considered potentially immortal. The current understanding how the germline escapes this otherwise inevitable phenomenon is outlined in this article.

Li, H. and Y. Cao (2018). "Karma or Immortality: Can Religion Influence Space-Time Mappings?" Cogn Sci 42(3): 1041-1056.

People implicitly associate the "past" and "future" with "front" and "back" in their minds according to their cultural attitudes toward time. As the temporal focus hypothesis (TFH) proposes, future-oriented people tend to think about time according to the future-in-front mapping, whereas past-oriented people tend to think about time according to the past-in-front mapping (de la Fuente, Santiago, Roman, Dumitrache, & Casasanto, 2014). Whereas previous studies have demonstrated that culture exerts an important influence on people's implicit spatializations of time, we focus specifically on religion, a prominent layer of culture, as potential additional influence on space-time mappings. In Experiment 1 and 2, we observed a difference between the two religious groups, with Buddhists being more past-focused and more frequently conceptualizing the past as ahead of them and the future as behind them, and Taoists more future-focused and exhibiting the opposite space-time mapping. In Experiment 3, we administered a religion prime, in which Buddhists were randomly assigned to visualize the picture of the Buddhas of the Past (Buddha Dipamkara) or the Future (Buddha Maitreya). Results showed that the pictorial icon of Dipamkara increased participants' tendency to conceptualize the past as in front of them. In contrast, the pictorial icon of Maitreya caused a dramatic increase in the rate of future-in-front responses. In Experiment 4, the causal effect of religion on implicit space-time mappings was replicated in atheists. Taken together, these findings provide converging evidence for the hypothesized causal role of religion for temporal focus in determining space-time mappings.

Liu, J. P. and R. Chen (2015). "Stressed SIRT7: facing a crossroad of senescence and immortality." Clin Exp Pharmacol Physiol 42(6): 567-569.

SIRT7 with coenzyme NAD catalyzes protein de-acetylation. In stress response, SIRT7 regulates protein folding in mitochondria with unknown mechanisms. Decreases in SIRT7 entrain hematopoietic stem cell senescence, but increasing SIRT7 causes elevation of hematopoietic stem cell regenerative function. We discuss the recent findings on SIRT7 and its binding proteins, NRF1 and GABPbeta1, in decision

making between the choices of inducing cell aging and immortality.

Lockwood, G. M. (2011). "Social egg freezing: the prospect of reproductive 'immortality' or a dangerous delusion?" Reprod Biomed Online 23(3): 334-340.

Until recently there was little to offer young women with cancer facing chemotherapy, radiotherapy or surgery and the probability of premature menopause and sterility. The first 'frozen egg' baby was born in 1986, but success rates were so low that egg freezing was neglected. Three technological developments in assisted reproduction treatment (intracytoplasmic sperm injection, dehydro-cryoprotectants and vitrification) have transformed this picture and now young women with frozen eggs have the same probability of a live birth per embryo transfer as women undergoing conventional IVF. For many women it is not cancer but the passage of time that denies them a chance of motherhood. Social, educational and financial pressures often lead them to delay starting a family until their late thirties, by which time the chance of success is compromised by low fecundity rates and an increased risk of miscarriage if they become pregnant. Donor eggs are not an option for many because of supply constraints and ethical concerns. Freezing a woman's eggs at age 30 literally 'freezes in time' her fertility potential and gives her the chance of a healthy pregnancy at a time of her choosing. The role of oocyte cryopreservation in the context of social egg freezing is discussed. Until recently there was little we could offer young women with cancer facing the chemotherapy, radiotherapy or surgery that could save their lives and the certainty of premature menopause and sterility. The first frozen-egg baby was born in 1986, but the success rate (100 eggs to produce one baby) was so low that egg freezing was neglected for years. Three technological developments in assisted reproduction treatment (intracytoplasmic sperm injection, dehydro-cryoprotectants and vitrification) have transformed this picture and now young women who have cryopreserved eggs can be offered the same chance of a live birth per embryo transfer as women undergoing conventional IVF treatment. For many women today it is not cancer but the simple passage of time that robs them of their chance of motherhood. Social, educational, emotional and financial pressures often lead them to delay trying to start a family until their late thirties, by which time the chance of success is very low. Women at age 40 face a 40% chance of miscarriage if they can get pregnant at all and by the age of 45, the risk of miscarriage is 75%. Donor eggs are not an option for many because of supply constraints and ethical and cultural concerns. Freezing a woman's eggs at age 30 literally 'freezes in time' her fertility potential and gives her the chance of a healthy pregnancy at a time of her choosing. This paper discusses the role of oocyte cryopreservation in the context of social egg freezing.

Loeb, L. (1926). "Transplantation and Potential Immortality of Mammalian Tissues." J Gen Physiol 8(5): 417-440.

1. Serial transplantation of tumors made it possible in 1901 and following years to draw the conclusion that various mammalian tissues have potential immortality. Serial transplantations of normal tissues did not succeed at first, because the homoioreaction on the part of the lymphocytes and connective tissue of the host injures the transplant. 2. In continuation of these experiments we found that cartilage of the rat can be transplanted serially to other rats at least for a period of 3 years. At the end of that time great parts of the transplanted cartilage and perichondrium are alive. 3. Not only the cartilage of young rats can be homoiotransplanted, but also the cartilage of very old rats which are nearing the end of life. By using such animals we have been able to obtain cartilage and perichondrium approaching an age of 6 years which is almost double the average age of a rat. 4. We found that cartilage can be homoiotransplanted more readily than other tissues for the following reasons: (a) While in principle the homoioreaction towards cartilage is the same as against other tissues, cartilage elicits this reaction with less intensity; (b) cartilage is better able to resist the invasion of lymphocytes and connective tissue than the majority of other tissues; (c) a gradual adaptation between transplant and host seems to take place in the case of cartilage transplantation, as a result of which the lymphocytic reaction on the part of the host tissue decreases progressively the longer the cartilage is kept in the strange host. 5. At time of examination we not only found living transplanted cartilage tissue, but also perichondrial tissue, which in response to a stimulus apparently originating in the necrotic central cartilage, had been proliferating and replacing it. These results suggest that it may perhaps be possible under favorable conditions to keep cartilage alive indefinitely through serial transplantations. 6. At the same time these experiments permit the analysis of the factors which are favorable or unfavorable to the continued life of the transplants. Favorable factors are: (a) Well preserved perichondrium around transplant; (b) cellular newly formed perichondrial cartilage-though it is doubtful whether such young cartilage cells allow a state of stable equilibrium. Host connective tissue does not invade transplant under these conditions. Unfavorable factors are: (a) Cartilage differentiation and the production of paraplastic substances (hyaline capsules in parts of transplant far removed from vessels and sources of oxygen and food; (b) cartilage necrosis when a still greater distance from nourishment exists; (c) disturbance of equilibrium between host connective

tissue and transplant due to above conditions, resulting in (d) attack by host connective tissue on transplanted cartilage, which is the chief danger in the preservation of the life of the whole transplant 7. It is pointed out that also in old age there exist similar problems of disturbances of tissue equilibria, due to degenerative changes in certain parenchymatous structures and to proliferative processes on the part of connective tissue and glia elements together with increase in paraplastic structures.

Loughran, O., et al. (1996). "Association of CDKN2A/p16INK4A with human head and neck keratinocyte replicative senescence: relationship of dysfunction to immortality and neoplasia." Oncogene 13(3): 561-568.

We have previously suggested that a gene mapping to chromosome 9p21 could contribute to replicative senescence and suppress cullular immortality in squamous neoplasia. Two candidate genes, the cyclin D1/cyclindependent kinase inhibitors CDKN2A/p16INK4A (p16) and CDKN2B/p15INK4B (p15) have now been identified in this region and we show here that p16 is upregulated when normal human keratinocytes undergo replicative senescence but not when they undergo differentiation. Furthermore, all of 19 immortal neoplastic keratinocyte head and neck lines, including nine showing loss of heterozygosity (LOH) at 9p21, showed undetectable p16 expression, whereas five of six senscent neoplastic cultures showed normal levels of expression. The retinoblastoma protein (pRb) appeared functional in all the cell lines and cultures examined. The mechanism of p16 inactivation appeared to be transcriptional silencing in 10 of 18 lines and homozygous deletions in the rest. Treatment of two of the immortal cell lines which had transcriptionally silent wild type p16 genes with 5aza-2deoxycytidine resulted in the re-expression of p16, thus implicating DNA methylation as one mechanism of transcriptional silencing in the immortal SCC-HN lines. We observed no cases of p16 point mutation. In contrast, the p15 gene was rarely transcriptionally silent and was not deleted in any of the cell lines which showed p16 deletions. Our results show that p16 dysfunction correlates strongly with keratinocyte immortalisation but less strongly with the stage of tumour progression. P16 dysfunction was not related to the neoplastic state or the length of time spent in vitro. The results also suggest that p16 but not p15 is involved in the keratinocyte replicative senescence programme. However, two neoplastic cell cultures which lacked p16 expression were still mortal, suggesting that the loss of p16 is a necessary but insufficient condition for human keratinocyte immortality.

Loxdale, H. D. and G. Lushai (2003). "Maintenance of aphid clonal lineages: images of immortality?" Infect Genet Evol 3(4): 259-269.

Artificial cloning and ancient asexuals have impacted upon both scientific and lay thinking in applied and theoretical fields as diverse as medicine and evolution. Hence, this is an opportune time to promote debate and discussion on what maintains a clonal lineage. The genetic fidelity of a clone has been discussed in detail elsewhere [Genet. Res. 79 (2002) 1; Biol. J. Linnean Soc. 79 (2003) 3]. In this paper, we focus on the lineage integrity (=longevity), or physiological lifespan of a clone with respect to senesce in relation to factors controlling telomere functioning. Aspects of cell line research pertinent to eukaryotic clonal lineages are discussed and, in particular, we try to extrapolate aspects of this research and apply it to apomictic (=mitotic) aphid lineages to suggest how they may be maintained. Analogies are made between single cells and individual aphids that senescence through a generation, whilst the respective lineages persist for finite periods, unless that is, compensatory mechanisms have evolved allowing immortality in the one and ancient asexuality in the other. Such comparison may allow fresh insights into the mechanisms of clonal lineage maintenance and evolution. We hypothesise that: (1). the cause of extinction in eukaryotic clonal lineages is due to deleterious effects on key regions of the genome, the chromosomal telomere being one such site; (2). recombination acts as a common mechanism to reset telomere functioning, perhaps more fundamental than its utility to reduce genetic load and maintain adaptability; and (3). ancient lineages persist through time as a function of group-specific compensatory mechanisms that maintain telomere integrity.

Loyd, A. L., et al. (2018). "Identifying the "Mushroom of Immortality": Assessing the Ganoderma Species Composition in Commercial Reishi Products." Front Microbiol 9: 1557.

Species of Ganoderma, commonly called reishi (in Japan) or lingzhi (in China), have been used in traditional medicine for thousands of years, and their use has gained interest from pharmaceutical industries in recent years. Globally, the taxonomy of Ganoderma species is chaotic, and the taxon name Ganoderma lucidum has been used for most laccate (shiny) Ganoderma species. However, it is now known that G. lucidum sensu stricto has a limited native distribution in Europe and some parts of China. It is likely that differences in the quality and quantity of medicinally relevant chemicals occur among Ganoderma species. To determine what species are being sold in commercially available products, twenty manufactured products (e.g., pills, tablets, teas, etc.) and seventeen grow your own (GYO) kits labeled as containing G. lucidum were analyzed. DNA was extracted, and the internal transcribed spacer (ITS) region and translation

elongation factor 1-alpha (tef1alpha) were sequenced with specific fungal primers. The majority (93%) of the manufactured reishi products and almost half of the GYO kits were identified as Ganoderma lingzhi. G. lingzhi is native to Asia and is the most widely cultivated and studied taxon for medicinal use. Illumina MiSeq sequencing of the ITS1 region was performed to determine if multiple Ganoderma species were present. None of the manufactured products tested contained G. lucidum sensu stricto, and it was detected in only one GYO kit. G. lingzhi was detected in most products, but other Ganoderma species were also present, including G. applanatum, G. australe, G. gibbosum, G. sessile, and G. sinense. Our results indicate that the content of these products vary and that better labeling is needed to inform consumers before these products are ingested or marketed as medicine. Of the 17 GYO kits tested, 11 kits contained Ganoderma taxa that are not native to the United States. If fruiting bodies of exotic Ganoderma taxa are cultivated, these GYO kits will likely end up in the environment. The effects of these exotic species to natural ecosystems needs investigation.

Mancini, A., et al. (2018). "Disruption of the beta1L Isoform of GABP Reverses Glioblastoma Replicative Immortality in a TERT Promoter Mutation-Dependent Manner." Cancer Cell 34(3): 513-528 e518.

TERT promoter mutations reactivate telomerase, allowing for indefinite telomere maintenance and enabling cellular immortalization. These mutations specifically recruit the multimeric ETS factor GABP, which can form two functionally independent transcription factor species: a dimer or a tetramer. We show that genetic disruption of GABPbeta1L (beta1L), a tetramer-forming isoform of GABP that is dispensable for normal development, results in TERT silencing in a TERT promoter mutation-dependent manner. Reducing TERT expression by disrupting beta1L culminates in telomere loss and cell death exclusively in TERT promoter mutant cells. Orthotopic xenografting of beta1L-reduced, TERT promoter mutant glioblastoma cells rendered lower tumor burden and longer overall survival in mice. These results highlight the critical role of GABPbeta1L in enabling immortality in TERT promoter mutant glioblastoma.

Manuelidis, E. E., et al. (1987). "Immortality of cell cultures derived from brains of mice and hamsters infected with Creutzfeldt-Jakob disease agent." Proc Natl Acad Sci U S A 84(3): 871-875.

Isolates from six patients with Creutzfeldt-Jakob disease (CJD) were injected into various strains of hamsters and mice, and the infective agent was propagated. Serially passaged cultures were established from these CJD agent-infected brains and from uninfected control brains. All healthy cultures (21 out of 21) from CJD agent-infected brains became immortal and/or transformed. In contrast only 3 out of 13 normal brain cultures became immortal, and the rest died out with serial propagation in vitro. The fact that permanent cell lines were readily derived from multiple rodent strains and all CJD isolates tested suggests that a transforming capability is an intrinsic property of CJD agents. This conclusion is supported by demonstrations of in vitro cell transformation by CJD infectious brain fractions. Although the molecular mechanism of transformation events associated with the CJD agent is not presently known, a provocative possibility is that the CJD agent has a direct effect on the host genome by mechanisms analogous to those known for slowly oncogenic retroviruses.

Maqsood, M. I., et al. (2013). "Immortality of cell lines: challenges and advantages of establishment." Cell Biol Int 37(10): 1038-1045.

Cellular immortality happens upon impairment of cell-cycle checkpoint pathways (p53/p16/pRb), reactivation or up-regulation of telomerase enzyme, or upregulation of some oncogenes or oncoproteins leading to a higher rate of cell division.There are also some other factors and mechanisms involved in immortalisation, which need to be discovered. Immortalisation of cells derived from different sources and establishment of immortal cell lines has proven useful in understanding the molecular pathways governing cell developmental cascades in eukaryotic, especially human, cells. After the breakthrough of achieving the immortal cells and understanding their critical importance in the field of molecular biology, intense efforts have been dedicated to establish cell lines useful for elucidating the functions of telomerase, developmental lineage of progenitors, self-renewal potency, cellular transformation, differentiation patterns and some bioprocesses, like odontogenesis. Meanwhile, discovering the exact mechanisms of immortality, a major challenge for science yet, is believed to open new gateways toward understanding and treatment of cancer in the long term. This review summarises the methods involved in establishing immortality, its advantages and the challenges still being faced in this field.

McLaren, A. (2001). "Mammalian germ cells: birth, sex, and immortality." Cell Struct Funct 26(3): 119-122.

The germ cell lineage in the mouse is not predetermined but is established during gastrulation, in response to signalling molecules acting on a subset of epiblast cells that move through the primitive streak together with extra-embryonic mesoderm precursors. After migration to the site of the future gonads, germ cell sex determination is achieved, with germ cell phenotype in male and female embryos diverging. Evidence suggests that all germ cells spontaneously

take the female pathway, entering prophase of the first meiotic division five or six days after the birth of the germ cell lineage, with the exception of those located in the embryonic testis, which exit the cell cycle in response to some inhibitory signal and remain in Go until after birth, when spermatogenesis begins. In culture, germ cells respond to certain growth factors by proliferating indefinitely. These immortalized embryonic germ (EG) cell lines are chromosomally stable and pluripotent, closely resembling the embryonic stem (ES) cell lines derived from blastocyst-stage embryos. Human EG and ES cell lines have recently been made, raising the hope that their differentiation could be directed to specific cell types, of value in the clinical treatment of degenerative diseases.

McNally, E. J., et al. (2019). "Long telomeres and cancer risk: the price of cellular immortality." J Clin Invest 129(9): 3474-3481.

The distribution of telomere length in humans is broad, but it has finite upper and lower boundaries. Growing evidence shows that there are disease processes that are caused by both short and long telomere length extremes. The genetic basis of these short and long telomere syndromes may be linked to mutations in the same genes, such as the telomerase reverse transcriptase (TERT), but through differential effects on telomere length. Short telomere syndromes have a predominant degenerative phenotype marked by organ failure that most commonly manifests as pulmonary fibrosis and are associated with a relatively low cancer incidence. In contrast, insights from studies of cancer-prone families as well as genome-wide association studies (GWAS) have identified both rare and common variants that lengthen telomeres as being strongly associated with cancer risk. We have hypothesized that these cancers represent a long telomere syndrome that is associated with a high penetrance of cutaneous melanoma and chronic lymphocytic leukemia. In this Review, we will synthesize the clinical and human genetic observations with data from mouse models to define the role of telomeres in cancer etiology and biology.

Medvedev, Z. A. (1981). "On the immortality of the germ line: genetic and biochemical mechanism. A review." Mech Ageing Dev 17(4): 331-359.

The nature of the differences between mortal somatic cells and immortal germ cell lines constitutes a major area of theoretical gerontology which has not yet received adequate attention. Weismann's theory, first stated almost exactly a century ago, was recently reconsidered by Kirkwood and Holliday. They applied modern concepts and findings on the factors regulating the accuracy of synthesis of macromolecules to explain germ line immortality. In the present paper, evidence on ageing of reproductive cells and the relationship of cytomorphogenetic events to periodic rejuvenation of germ cell lines is summarized and evaluated. Key events include the elimination or reversal of some DNA changes in germ cells through recombination and meiotic haploidization, cyclic regeneration of transcriptional and translational systems during gametogenesis and early development, and the selection of stable, viable genomes at various stages of the reproductive cycle. These rejuvenatory processes are compared and related to molecular events which differentiated somatic cells are unable to carry out.

Meeker, A. K. and D. S. Coffey (1997). "Telomerase: a promising marker of biological immortality of germ, stem, and cancer cells. A review." Biochemistry (Mosc) 62(11): 1323-1331.

This review will describe the current state of knowledge of telomerase as it relates to human malignancies, focusing primarily on published measurements of this enzymes activity in benign and malignant neoplasms and their normal tissue counterparts. Key questions concerning the potential clinical utility of assaying for telomerase activity will be addressed and the implications of recent findings discussed.

Mummery, C. (2004). "Stem cell research: immortality or a healthy old age?" Eur J Endocrinol 151 Suppl 3: U7-12.

Stem cell research holds the promise of treatments for many disorders resulting from disease or trauma where one or at most a few cell types have been lost or do not function. In combination with tissue engineering, stem cells may represent the greatest contribution to contemporary medicine of the present century. Progress is however being hampered by the debate on the origin of stem cells, which can be derived from human embryos and some adult tissues. Politics, religious beliefs and the media have determined society's current perception of their relative value while the ethical antipathy towards embryonic stem cells, which require destruction of a human embryo for their derivation, has in many countries biased research towards adult stem cells. Many scientists believe this bias may be premature and basic research on both cell types is still required. The media has created confusion about the purpose of stem cell research: treating chronic ailments or striving for immortality. Here, the scientific state of the art on adult and embryonic stem cells is reviewed as a basis for a debate on whether research on embryonic stem cells is ethically acceptable.

Munne-Bosch, S. (2014). "Perennial roots to immortality." Plant Physiol 166(2): 720-725.

Maximum lifespan greatly varies among species, and it is not strictly determined; it can change with species evolution. Clonal growth is a major factor governing maximum lifespan. In the plant kingdom,

the maximum lifespans described for clonal and nonclonal plants vary by an order of magnitude, with 43,600 and 5,062 years for Lomatia tasmanica and Pinus longaeva, respectively. Nonclonal perennial plants (those plants exclusively using sexual reproduction) also present a huge diversity in maximum lifespans (from a few to thousands of years) and even more interestingly, contrasting differences in aging patterns. Some plants show a clear physiological deterioration with aging, whereas others do not. Indeed, some plants can even improve their physiological performance as they age (a phenomenon called negative senescence). This diversity in aging patterns responds to species-specific life history traits and mechanisms evolved by each species to adapt to its habitat. Particularities of roots in perennial plants, such as meristem indeterminacy, modular growth, stress resistance, and patterns of senescence, are crucial in establishing perenniality and understanding adaptation of perennial plants to their habitats. Here, the key role of roots for perennial plant longevity will be discussed, taking into account current knowledge and highlighting additional aspects that still require investigation.

Murphy, N. (2011). "Immortality versus resurrection in the Christian tradition." Ann N Y Acad Sci 1234: 76-82.

For those in contemporary society who believe in an afterlife, there are a number of views available. The most common may be based on belief in an immortal soul. However, the early Christian account was, instead, bodily resurrection. As Christianity moved throughout the Mediterranean world, apologists and theologians adapted their teaching on human nature and the afterlife to Greek and Roman philosophies. By the time of Augustine (d. 430), the doctrines of body-soul dualism and immortality of the soul were firmly entrenched in Christian teaching. The incorporation of the concept of an immortal soul into Christian accounts of life after death produced a hybrid account. The body dies, the soul (at least of those who were to be saved) travels to heaven. At the end of history, there would be a general resurrection, and the souls would be reunited with their bodies, although the bodies would be in a transformed, indestructible state. This hybrid account of life after death went largely uncontested until the twentieth century. In this essay, I describe this history and argue for a return to the early Christian view of humans as a unity, not a duality, and for belief in resurrection of the body as the appropriate expectation for eternal life. This would not only be truer to Christian sources, but, valuable, I believe, in focusing Christian attention on the need to care for the environment.

Olshansky, S. J. and B. A. Carnes (2013). "Zeno's Paradox of Immortality." Gerontology 59(1): 85-92.

Scientists who speculate on the future of human longevity have a broad range of views ranging from the promise of immortality, to radical life extension, to declines in life expectancy. Among those who contend that radical life extension is already here, or on the horizon, or immortality is forthcoming, elements of their reasoning appear surprisingly close, if not identical, to a famous mathematical paradox posed by the ancient Greek mathematician known as Zeno. Here we examine the underlying assumptions behind the views that much longer life expectancies are forthcoming or have already arrived, and place their line of reasoning within the context of a new Zeno paradox described here as The Paradox of Immortality.

Petralia, R. S., et al. (2014). "Aging and longevity in the simplest animals and the quest for immortality." Ageing Res Rev 16: 66-82.

Here we review the examples of great longevity and potential immortality in the earliest animal types and contrast and compare these to humans and other higher animals. We start by discussing aging in single-celled organisms such as yeast and ciliates, and the idea of the immortal cell clone. Then we describe how these cell clones could become organized into colonies of different cell types that lead to multicellular animal life. We survey aging and longevity in all of the basal metazoan groups including ctenophores (comb jellies), sponges, placozoans, cnidarians (hydras, jellyfish, corals and sea anemones) and myxozoans. Then we move to the simplest bilaterian animals (with a head, three body cell layers, and bilateral symmetry), the two phyla of flatworms. A key determinant of longevity and immortality in most of these simple animals is the large numbers of pluripotent stem cells that underlie the remarkable abilities of these animals to regenerate and rejuvenate themselves. Finally, we discuss briefly the evolution of the higher bilaterians and how longevity was reduced and immortality lost due to attainment of greater body complexity and cell cycle strategies that protect these complex organisms from developing tumors. We also briefly consider how the evolution of multiple aging-related mechanisms/pathways hinders our ability to understand and modify the aging process in higher organisms.

Piper, S. L., et al. (2012). "Inducible immortality in hTERT-human mesenchymal stem cells." J Orthop Res 30(12): 1879-1885.

Human mesenchymal stem cells (hMSCs) are attractive candidates for tissue engineering and cell-based therapy because of their multipotentiality and availability in adult donors. However, in vitro expansion and differentiation of these cells is limited by replicative senescence. The proliferative capacity of hMSCs can be enhanced by ectopic expression of telomerase, allowing for long-term culture. However, hMSCs with constitutive telomerase expression demonstrate unregulated growth and even tumor

formation. To address this problem, we used an inducible Tet-On gene expression system to create hMSCs in which ectopic telomerase expression can be induced selectively by the addition of doxycycline (i-hTERT hMSCs). i-hTERT hMSCs have inducible hTERT expression and telomerase activity, and are able to proliferate significantly longer than wild type hMSCs when hTERT expression is induced. They stop proliferating when hTERT expression is turned off and can be rescued when expression is re-induced. They retain multipotentiality in vitro even at an advanced age. We also used a selective inhibitor of telomere elongation to show that the mechanism driving immortalization of hMSCs by hTERT is dependent upon maintenance of telomere length. Thanks to their extended lifespan, preserved multipotentiality and controlled growth, i-hTERT hMSCs may prove to be a useful tool for the development and testing of novel stem cell therapies.

Podgorny, I. (2011). "Modern embalming, circulation of fluids, and the voyage through the human arterial system: Carl L. Barnes and the culture of immortality in America." Nuncius 26(1): 109-131.

By considering the work of American embalmer, lawyer, and physician Carl Lewis Barnes (1872-1927), this paper analyzes the emergence of modern embalming in America. Barnes experimented with and exhibited the techniques by which embalming fluids travelled into the most remote cavities of the human body. In this sense, modem embalmers based their skills and methods on experimental medicine, turning the anatomy of blood vessels, physiology of circulation, and composition of blood into a circuit that allowed embalming fluids to move throughout the corpse. Embalmers in the late 19th century took ownership of the laws of hydrodynamics and the physiology of blood circulation to market their fluids and equipment, thus playing the role of physiologists of death, performing and demonstrating physiological experiments with dead bodies.

Proenca, A. M., et al. (2019). "Cell aging preserves cellular immortality in the presence of lethal levels of damage." PLoS Biol 17(5): e3000266.

Cellular aging, a progressive functional decline driven by damage accumulation, often culminates in the mortality of a cell lineage. Certain lineages, however, are able to sustain long-lasting immortality, as prominently exemplified by stem cells. Here, we show that Escherichia coli cell lineages exhibit comparable patterns of mortality and immortality. Through single-cell microscopy and microfluidic techniques, we find that these patterns are explained by the dynamics of damage accumulation and asymmetric partitioning between daughter cells. At low damage accumulation rates, both aging and rejuvenating lineages retain immortality by reaching their respective states of physiological equilibrium. We show that both asymmetry and equilibrium are present in repair mutants lacking certain repair chaperones, suggesting that intact repair capacity is not essential for immortal proliferation. We show that this growth equilibrium, however, is displaced by extrinsic damage in a dosage-dependent response. Moreover, we demonstrate that aging lineages become mortal when damage accumulation rates surpass a threshold, whereas rejuvenating lineages within the same population remain immortal. Thus, the processes of damage accumulation and partitioning through asymmetric cell division are essential in the determination of proliferative mortality and immortality in bacterial populations. This study provides further evidence for the characterization of cellular aging as a general process, affecting prokaryotes and eukaryotes alike and according to similar evolutionary constraints.

Qi, W., et al. (2021). "The secreted endoribonuclease ENDU-2 from the soma protects germline immortality in C. elegans." Nat Commun 12(1): 1262.

Multicellular organisms coordinate tissue specific responses to environmental information via both cell-autonomous and non-autonomous mechanisms. In addition to secreted ligands, recent reports implicated release of small RNAs in regulating gene expression across tissue boundaries. Here, we show that the conserved poly-U specific endoribonuclease ENDU-2 in C. elegans is secreted from the soma and taken-up by the germline to ensure germline immortality at elevated temperature. ENDU-2 binds to mature mRNAs and negatively regulates mRNA abundance both in the soma and the germline. While ENDU-2 promotes RNA decay in the soma directly via its endoribonuclease activity, ENDU-2 prevents misexpression of soma-specific genes in the germline and preserves germline immortality independent of its RNA-cleavage activity. In summary, our results suggest that the secreted RNase ENDU-2 regulates gene expression across tissue boundaries in response to temperature alterations and contributes to maintenance of stem cell immortality, probably via retaining a stem cell specific program of gene expression.

Rablen, M. D. and A. J. Oswald (2008). "Mortality and immortality: the Nobel Prize as an experiment into the effect of status upon longevity." J Health Econ 27(6): 1462-1471.

It has been known for centuries that the rich and famous have longer lives than the poor and ordinary. Causality, however, remains trenchantly debated. The ideal experiment would be one in which extra status could somehow be dropped upon a sub-sample of individuals while those in a control group of comparable individuals received none. This paper

attempts to formulate a test in that spirit. It collects 19th-century birth data on science Nobel Prize winners. Correcting for potential biases, we estimate that winning the Prize, compared to merely being nominated, is associated with between 1 and 2 years of extra longevity.

Rahman, R., et al. (2009). "Cellular immortality in brain tumours: an integration of the cancer stem cell paradigm." Biochim Biophys Acta 1792(4): 280-288.

Brain tumours are a diverse group of neoplasms that continue to present a formidable challenge in our attempt to achieve curable intervention. Our conceptual framework of human brain cancer has been redrawn in the current decade. There is a gathering acceptance that brain tumour formation is a phenotypic outcome of dysregulated neurogenesis, with tumours viewed as abnormally differentiated neural tissue. In relation, there is accumulating evidence that brain tumours, similar to leukaemia and many solid tumours, are organized as a developmental hierarchy which is maintained by a small fraction of cells endowed with many shared properties of tissue stem cells. Proof that neurogenesis persists throughout adult life, compliments this concept. Although the cancer cell of origin is unclear, the proliferative zones that harbour stem cells in the embryonic, post-natal and adult brain are attractive candidates within which tumour-initiation may ensue. Dysregulated, unlimited proliferation and an ability to bypass senescence are acquired capabilities of cancerous cells. These abilities in part require the establishment of a telomere maintenance mechanism for counteracting the shortening of chromosomal termini. A strategy based upon the synthesis of telomeric repeat sequences by the ribonucleoprotein telomerase, is prevalent in approximately 90% of human tumours studied, including the majority of brain tumours. This review will provide a developmental perspective with respect to normal (neurogenesis) and aberrant (tumourigenesis) cellular turnover, differentiation and function. Within this context our current knowledge of brain tumour telomere/telomerase biology will be discussed with respect to both its developmental and therapeutic relevance to the hierarchical model of brain tumourigenesis presented by the cancer stem cell paradigm.

Raia, C. G. (2007). "From ether theory to ether theology: Oliver Lodge and the physics of immortality." J Hist Behav Sci 43(1): 18-43.

This article follows the development of physicist Oliver Lodge's religio-scientific worldview, beginning with his reticent attraction to metaphysics in the early 1880s to the full formulation of his "ether theology" in the late 1890s. Lodge undertook the study of psychical phenomena such as telepathy, telekinesis, and "ectoplasm" to further his scientific investigations of the ether, speculating that electrical and psychical manifestations were linked phenomena that described the deeper underlying structures of the universe, beneath and beyond matter. For Lodge, to fully understand the ether was to force from the universe an ultimate Revelation, and psychical research, as the most modern and probatory science, was poised to replace religion as the means of that disclosure.

Rando, T. A. (2006). "Stem cells, ageing and the quest for immortality." Nature 441(7097): 1080-1086.

Adult stem cells reside in most mammalian tissues, but the extent to which they contribute to normal homeostasis and repair varies widely. There is an overall decline in tissue regenerative potential with age, and the question arises as to whether this is due to the intrinsic ageing of stem cells or, rather, to the impairment of stem-cell function in the aged tissue environment. Unravelling these distinct contributions to the aged phenotype will be critical to the success of any therapeutic application of stem cells in the emerging field of regenerative medicine with respect to tissue injury, degenerative diseases or normal functional declines that accompany ageing.

Rao, M. (2002). "Fatal promise of immortality." J Indian Med Assoc 100(1): 31-32, 36.

The Census of 2001 brings the heartening news that the secular decline in the sex ratio of file population has come to a halt: The sex ratio in the population has increased from 927 females per thousand males to 933 females per thousand males in 2001. However it also brings disturbing figures of the continuing decline in the sex ratio in the 0-6 years age group. Partly due to higher female mortality in this age group, demographers had agreed that it is also due to female foeticide, the sex-selective abortion of female foetuses. The figure for the number of females per 1000 males has come down from 945 in 1991 to 927 in 2001. Some states in the country, Himachal Pradesh, with a decline of 54, Punjab of 82, Haryana of 59, and Delhi and Gujarat of 50 each, have shown more precipitous declines. Indeed the sex ratio at birth, based on the SRS, points to an increasing masculinisation from 109.5 males per 100 females in 1990 to 111.0 males per 100 females in 1998. As a consequence there has been a great deal of official concern, the Indian Medical Association initiated a campaign to sensitise the public, the Supreme Court has instructed states to implement the Prenatal Diagnostic Techniques (PNDA) Act, and so-called religious leaders have too entered the fray. The situation is complex: Prenatal sex diagnostic tests are increasingly available, prospective parents apparently want it. A section of the medical profession, which supplies these services, argues that they reflect the values of society and are merely meeting the demands of women. It is in this context that Amin Malouf's excellent novel 'The Century after

Beatrice' should perhaps be made essential reading for medical students, indeed all medical professionals.

Rauser, C. L., et al. (2003). "Aging, fertility, and immortality." Exp Gerontol 38(1-2): 27-33.

Evolutionary theory suggests that fecundity rates will plateau late in life in the same fashion as mortality rates. We demonstrate that late-life plateaus arise for fecundity in Drosophila melanogaster. The result qualitatively fits the evolutionary theory of late life based on the force of natural selection. But there are a number of alternative interpretations. Fecundity plateaus could be secondary consequences of mortality-rate plateaus. Female fecundity plateaus might arise from diminished male sexual function. Another alternative hypothesis is analogous to male sexual inadequacy: nutritional shortfalls. These may arise later in life because of a decline in female feeding or digestion. If some females have a life-long tendency to lay eggs at a faster rate, but die earlier, then aging for fecundity could arise from the progressive loss of the fast-layers, with the late-life plateau simply the laying patterns of individual females who were slow-layers throughout adult life. If this type of model is generally applicable to late life, then we should find that the females who survive to lay at a slow but steady rate in late life have a similar laying pattern in mid-life.

Robinson, N. J., et al. (2019). "Stem cells, immortality, and the evolution of metastatic properties in breast cancer: telomere maintenance mechanisms and metastatic evolution." J Cancer Metastasis Treat 5.

Breast cancer is the most significant cause of cancer-related death in women around the world. The vast majority of breast cancer-associated mortality stems from metastasis, which remains an incurable disease state. Metastasis results from evolution of clones that possess the insidious properties required for dissemination and colonization of distant organs. These clonal populations are descended from breast cancer stem cells (CSCs), which are also responsible for their prolonged maintenance and continued evolution. Telomeres impose a lifespan on cells that can be extended when they are actively elongated, as occurs in CSCs. Thus, changes in telomere structure serve to promote the survival of CSCs and subsequent metastatic evolution. The selection of telomere maintenance mechanism (TMM) has important consequences not only for CSC survival and evolution, but also for their coordination of various signaling pathways that choreograph the metastatic cascade. Targeting the telomere maintenance machinery may therefore provide a boon to the treatment of metastatic breast cancer. Here we review the two major TMMs and the roles they play in the development of stem and metastatic breast cancer cells. We also highlight current and future approaches to targeting these mechanisms in clinical settings to alleviate metastatic breast cancers.

Ryan, P. A., et al. (1994). "Failure of infinite life span human cells from different immortality complementation groups to yield finite life span hybrids." J Cell Physiol 159(1): 151-160.

The observation that fusion of infinite life span cells with finite life span cells produces hybrid cells with finite life spans led to the conclusion that an infinite life span in culture is a recessive trait resulting from loss of the function of a gene or genes that contribute to an active program for cellular senescence. Furthermore, finding that certain pairs of infinite life span cells, when fused to one another, can complement each other to yield finite life span hybrids allowed 30 infinite life span cell lines to be assigned to four immortality complementation groups (Pereira-Smith and Smith, 1988, Proc. Natl. Acad. Sci. U.S.A., 85:6042). In the present study, we fused a chromosomally stable, near diploid, morphologically normal, infinite life span cell strain, designated MSU-1.1, with its normal, finite life span, precursor cell strain and obtained finite life span hybrids, as expected if infinite life span in culture is a recessive trait. However, 14 of the 14 hybrids from our fusions of MSU-1.1 cells with representative cell lines from each of the four immortality complementation groups, and 38 of the 39 hybrids from our fusions of infinite life span cells that have been reported to complement each other, failed to exhibit finite life spans. This result suggests that infinite life span cells cannot complement each other to yield finite life span hybrids. In examining this unexpected result, we obtained evidence that long-term dual drug selection can be deleterious to hybrid cells even though they carry resistance markers for both drugs, indicating that the cell death of such hybrids observed in other studies may have resulted from the cytotoxic effect of long-term drug selection, rather than from senescence.

Saini, A., et al. (2013). "'From death, lead me to immortality' - mantra of ageing skeletal muscle." Curr Genomics 14(4): 256-267.

Skeletal muscle is a post-mitotic tissue maintained by repair and regeneration through a population of stem cell-like satellite cells. Following muscle injury, satellite cell proliferation is mediated by local signals ensuring sufficient progeny for tissue repair. Age-related changes in satellite cells as well as to the local and systemic environment potentially impact on the capacity of satellite cells to generate sufficient progeny in an ageing organism resulting in diminished regeneration. 'Rejuvenation' of satellite cell progeny and regenerative capacity by environmental stimuli effectors suggest that a subset of age-dependent satellite cell changes may be reversible. Epigenetic regulation of satellite stem cells that include DNA methylation and histone modifications which regulate gene expression are potential mechanisms for such

reversible changes and have been shown to control organismal longevity. The area of health and ageing that is likely to benefit soonest from advances in the biology of adult stem cells is the emerging field of regenerative medicine. Further studies are needed to elucidate the mechanisms by which epigenetic modifications regulate satellite stem cell function and will require an increased understanding of stem-cell biology, the environment of the aged tissue and the interaction between the two.

Sakaguchi, A., et al. (2014). "Caenorhabditis elegans RSD-2 and RSD-6 promote germ cell immortality by maintaining small interfering RNA populations." Proc Natl Acad Sci U S A 111(41): E4323-4331.

Germ cells are maintained in a pristine non-aging state as they proliferate over generations. Here, we show that a novel function of the Caenorhabditis elegans RNA interference proteins RNAi spreading defective (RSD)-2 and RSD-6 is to promote germ cell immortality at high temperature. rsd mutants cultured at high temperatures became progressively sterile and displayed loss of small interfering RNAs (siRNAs) that target spermatogenesis genes, simple repeats, and transposons. Desilencing of spermatogenesis genes occurred in late-generation rsd mutants, although defective spermatogenesis was insufficient to explain the majority of sterility. Increased expression of repetitive loci occurred in both germ and somatic cells of late-generation rsd mutant adults, suggesting that desilencing of many heterochromatic segments of the genome contributes to sterility. Nuclear RNAi defective (NRDE)-2 promotes nuclear silencing in response to exogenous double-stranded RNA, and our data imply that RSD-2, RSD-6, and NRDE-2 function in a common transgenerational nuclear silencing pathway that responds to endogenous siRNAs. We propose that RSD-2 and RSD-6 promote germ cell immortality at stressful temperatures by maintaining transgenerational epigenetic inheritance of endogenous siRNA populations that promote genome silencing.

Saltzman, A. L., et al. (2018). "Multiple Histone Methyl-Lysine Readers Ensure Robust Development and Germline Immortality in Caenorhabditis elegans." Genetics 210(3): 907-923.

Chromatin modifications, including methylation of histone H3 at lysine 27 (H3K27me) by the Polycomb group proteins, play a broadly conserved role in the maintenance of cell fate. Diverse chromatin organization modifier (chromo) domain proteins act as "readers" of histone methylation states. However, understanding the functional relationships among chromo domains and their roles in the inheritance of gene expression patterns remains challenging. Here, we identify two chromo-domain proteins, CEC-1 and CEC-6, as potential readers of H3K27me in Caenorhabditis elegans, where they have divergent expression patterns and contribute to distinct phenotypes. Both cec-1 and cec-6 genetically interact with another chromo-domain gene, cec-3, a reader of H3K9 methylation. Combined loss of cec-1 and cec-3 leads to developmental defects in the adult that result in decreased fitness. Furthermore, loss of cec-6 and cec-3 surprisingly leads to a progressive loss of fertility across generations, a "mortal germline" phenotype. Our results provide evidence of functional compensation between H3K27me and H3K9me heterochromatin pathways, and show that histone methylation readers contribute to both somatic development and transgenerational fitness.

Scott, A., et al. (2021). "Long live A(me)rica! An examination of the interplay between nationalistic-symbolic immortality striving and belief in life after death." J Pers Soc Psychol 120(4): 861-881.

Terror management theory (TMT) proposes that the awareness of our eventual death is at odds with our evolved desire to live and that humans attempt to resolve this psychological conflict by investing in cultural worldviews that grant symbolic or literal immortality. The present studies examine the interplay between symbolic and literal immortality striving. Three studies show that, following a death reminder, only individuals who did not have a route to literal immortality (belief in an afterlife) increased how long they believe their culture (Canada in Studies 1 and 2, the United States in Study 3), will last by thousands of years. Study 4 demonstrated that this moderation effect cannot be explained by general religiosity; Study 5 conceptually replicated this finding using a different measure of perceived cultural longevity. Finally, Study 6 demonstrates that for those who were highly invested in their nation but did not believe in an afterlife, perceived cultural longevity was associated with decreased death anxiety. These results are consistent with the notion that people possess a primary path to immortality that follows directly from their worldview. The need for increased specificity in study design in TMT and the threat and defense literature more broadly is discussed. (PsycInfo Database Record (c) 2021 APA, all rights reserved).

Shammas, M. A., et al. (1999). "Telomerase inhibition by peptide nucleic acids reverses 'immortality' of transformed human cells." Oncogene 18(46): 6191-6200.

Telomerase activity, the ability to add telomeric repeats to the ends of chromosomes, has been detected in most immortal cell lines including tumor cells, but is low or absent in most diploid, mortal cells such as those of somatic tissues. Peptide nucleic acids (PNAs), analogs of DNA or RNA which bind to complementary nucleic acids with very high affinity, were co-electroporated into immortal human cells

along with a selectable plasmid. Introduction of PNAs inverse-complementary to telomerase RNA effectively inhibited telomerase activity in intact cells, shortened telomeres, reduced colony size, and arrested cell proliferation after a lag period of 5-30 cell generations, consistent with suppression of their 'immortality'. Electroporation of selection plasmid alone had no effect, while PNAs of altered sequence were markedly less effective in each assay. This constitutes the first demonstration of cell growth arrest through telomerase inhibition, upon treatment of intact cells with an exogenous compound which can be efficiently delivered in vivo. The phenotype of telomerase-inhibited transformed cells differs from senescence of normal diploid fibroblasts, but rather resembles the crisis state of incompletely transformed cells.

Smelick, C. and S. Ahmed (2005). "Achieving immortality in the C. elegans germline." Ageing Res Rev 4(1): 67-82.

Germline immortality is a topic that has intrigued theoretical biologists interested in aging for over a century. The germ cell lineage can be passed from one generation to the next, indefinitely. In contrast, somatic cells are typically only needed for a single generation and are then discarded. Germ cells may, therefore, harbor rejuvenation mechanisms that enable them to proliferate for eons. Such processes are thought to be either absent from or down-regulated in somatic cells, although cell non-autonomous forms of rejuvenation are formally possible. A thorough description of mechanisms that foster eternal youth in germ cells is lacking. The mysteries of germline immortality are being addressed in the nematode Caenorhabditis elegans by studying mutants that reproduce normally for several generations but eventually become sterile. The mortal germline mutants probably become sterile as a consequence of accumulating various forms of heritable cellular damage. Such mutants are abundant, indicating that several different biochemical pathways are required to rejuvenate the germline. Thus, forward genetics should help to define mechanisms that enable the germline to achieve immortality.

Soady, K. and M. J. Smalley (2012). "Slugging their way to immortality: driving mammary epithelial cells into a stem cell-like state." Breast Cancer Res 14(5): 319.

Delineating the molecular factors that define and maintain the mammary stem cell state is vital for understanding normal development and tumourigenesis. A recent study by Guo and colleagues identifies two master transcriptional regulators of mammary stem cells, Slug and Sox9, ectopic expression of which confers stem cell attributes on differentiated mammary epithelial cells. Slug and Sox9 expression was also shown to determine in vivo metastatic potential of human breast cancer cell lines. Understanding these factors in the context of normal lineage differentiation is an important step toward elucidating the mammary epithelial cell hierarchy and the origins of cancer stem cells.

Solinas-Toldo, S., et al. (1997). "Specific chromosomal imbalances in human papillomavirus-transfected cells during progression toward immortality." Proc Natl Acad Sci U S A 94(8): 3854-3859.

High risk human papillomaviruses (HPVs) known to be closely associated with cervical cancer, such as HPV16 and HPV18, have the potential to immortalize human epithelial cells in culture. Four lines of HPV-transfected keratinocytes were analyzed by comparative genomic hybridization at different time points after transfection. A number of chromosomal imbalances was found to be highly characteristic for the cultures progressing toward immortality. Whereas several of these were new and previously not found as recurrent aberrations in cervical tumors, some were identical to chromosomal changes observed during cervical carcinogenesis. The data put new emphasis on the studied cell system as a relevant model for HPV-induced pathogenesis.

Soo, J. K., et al. (2011). "Malignancy without immortality? Cellular immortalization as a possible late event in melanoma progression." Pigment Cell Melanoma Res 24(3): 490-503.

Cell senescence is a permanent growth arrest following extended proliferation. Cultured cancer cells including metastatic melanoma cells often appear immortal (proliferate indefinitely), while uncultured benign nevi (moles) show senescence markers. Here, with new explantation methods, we investigated which classes of primary pigmented lesions are typically immortal. Nevi yielded a few proliferating cells, consistent with most nevus cells being senescent. No nevus culture (0/28) appeared immortal. Some thin and thick melanoma cultures proved immortal under these conditions, but surprisingly few (4/37). All arrested cultures displayed three senescence markers in some cells: beta-galactosidase, nuclear p16, and heterochromatic foci/aggregates. However, melanoma cultures also showed features of telomeric crisis (arrest because of ultrashort telomeres). Moreover, crisis markers including anaphase bridges were frequent in uncultured vertical growth-phase (VGP) melanomas. Conversely, all immortal melanoma cultures expressed telomerase reverse transcriptase and telomerase, showing aneuploidy. The findings suggest that primary melanomas are typically precrisis, with immortalization/telomere maintenance as a late event.

Soundararajan, V., et al. (2010). "Multifunctional nanoscale platforms for targeting of the cancer cell immortality spectrum." Macromol Rapid Commun 31(2): 202-216.

In the post-genomic era, "omics" platforms and cancer systems biology are greatly advancing our knowledge of the molecular and cellular underpinnings of cancer. In this article, we begin by outlining the factors governing the development of cancer (tumorigenesis) and use this framework to motivate the need for systems-approaches to cancer diagnostics and therapeutics. We review recent efforts to tap into the remarkable potential of nanotechnology for (i) systems-surveillance (or "sensing") of the molecular signatures of tumorigenesis, and (ii) spatiotemporally-regulated delivery (or "targeting") of combination therapeutics to cancer cells. Specifically, we highlight the salient role of polymeric biomaterials and describe the physicochemical characteristics that render them attractive for the design of such nanoscale platforms. We conclude with discussions on the emerging role of macromolecular biophysics and computational nanotechnology in engineering spatiotemporally-regulated anti-cancer systems.

Spiering, A. L., et al. (1991). "Correlation between complementation group for immortality and DNA synthesis inhibitors." Exp Cell Res 195(2): 541-545.

Previous studies had demonstrated that a DNA synthesis inhibitor(s) was produced by senescent but not young human diploid fibroblasts (HDF). Analysis of immortal human cell lines led to the finding that SUSM-1, carcinogen-treated immortal human liver fibroblast cells, expressed a potent inhibitor of DNA synthesis that was active in proliferation-competent young HDF but did not affect the SUSM-1 cell line itself. To determine whether one mechanism of escape from senescence to the immortal phenotype involved the loss of response to such DNA synthesis inhibitors, we initiated the present study analyzing a larger number of immortal human cell lines representative of the four complementation groups for indefinite division identified to date. We have found a correlation between the assignment of a cell line to Complementation Group D and the production of DNA synthesis inhibitors coupled with inability to respond to the inhibitory factors. We have also observed a correlation between the ability of immortal cell lines to respond to such DNA synthesis inhibitory factors and assignment to Complementation Group B. These data suggest DNA synthesis inhibitors are involved in the limited lifespan of normal cells and that the immortalization process may involve alterations in the activity of or response to such inhibitors.

Spiro, C., et al. (1988). "A tagged helper-free Friend virus causes clonal erythroblast immortality by specific proviral integration in the cellular genome." J Virol 62(11): 4129-4135.

A colinear molecular clone of the Lilly-Steeves polycythemia strain of Friend spleen focus-forming virus (SFFV) was modified by inserting a 215-base-pair tag of simian virus 40 DNA into its nonfunctional pol gene region. The DNA was then transfected into psi-2 packaging cells, and helper-free tagged SFFV was recovered in the culture medium. Injection of this helper-free virus into NIH/Swiss mice caused transient mild splenomegaly and formation of spleen foci at 9 to 10 days. Although the vast majority of infected erythroblast clones then differentiated and died out, rare cell clones that were present in only 20 to 30% of the mice grew extensively by 26 to 33 days to form transplantable leukemias. The clonality of these leukemias was established by Southern blot analysis of their DNAs by using several restriction endonucleases and the simian virus 40 tag as a hybridization probe. All transplantable leukemias lacked helper virus contamination and contained a single tagged SFFV provirus that expressed the mitogenic env gene product gp55. The SFFV proviruses in these leukemias also appeared to be integrated into a few tightly clustered sites in the cellular genome. Although the tagged SFFV caused polycythemia during the polyclonal early stage of erythroblastosis, growth of the helper-free clonal erythroleukemias caused severe anemia. These results suggest that a single SFFV can cause mitosis of erythroblasts, and that cell immortalization also occurs when the provirus integrates into a critical site in the host genome. We propose that mice with clonal-stage leukemia become anemic because the immortalizing proviral integrations interfere with the cellular commitment to differentiate.

Steenbergen, R. D., et al. (1996). "Transition of human papillomavirus type 16 and 18 transfected human foreskin keratinocytes towards immortality: activation of telomerase and allele losses at 3p, 10p, 11q and/or 18q." Oncogene 13(6): 1249-1257.

This study aimed at resolving cellular genetic alterations in the process of in vitro immortalization of human keratinocytes by human papillomavirus (HPV) types 16 and 18. Four cell lines of primary human foreskin keratinocytes transfected with HPV 16 and HPV 18, respectively, were analysed during the transition from the mortal to immortal state. All cell lines showed strong telomerase activity at the immortal state, whereas no or only weak telomerase activity was detected in mortal precursor cells. This was consistent with telomere stabilization or restoration only observed in immortal cells. HPV physical state and copy number appeared constant during immortalization and HPV E6/E7 transcripts were present throughout. Immortalization was associated with clonal allele losses at 3p combined with either 11q or 18q or at 10p, dependent on the cell line. Moreover, a correlation was evident between the onset of telomerase activity and allele loss at 3p or 10p. All immortalized cells retained the capability to differentiate after growth in the presence of physiological calcium and serum.

Moreover, one of the immortal cell lines displayed terminal differentiation after organotypic culturing on collagen rafts. The data suggest that (a) several pathways exist for HPV mediated immortalization that may involve genes residing at 3p, 10p, 11q and/or 18q; (b) 3p and 10p may encode genes involved in telomerase regulation; and (c) immortalization in vitro can be correlated with a spectrum of morphological changes varying from mild to severe dysplasia.

Stolzing, A., et al. (2007). "Fusion and regenerative therapies: is immortality really recessive?" Rejuvenation Res 10(4): 571-586.

Harnessing cellular fusion as a potential tool for regenerative therapy has been under tentative investigation for decades. A look back the history of fusion experiments in gerontology reveals that whereas some studies indicate that aging-related changes are conserved in fused cells, others have demonstrated that fusion can be used as a tool to revoke cellular senescence and induce tissue regeneration. Recent findings about the role of fusion processes in tissue homeostasis, replenishment, and repair link insights from fusion studies of previous decades with modern developments in stem cell biology and regenerative medicine. We suggest that age-associated loss of regenerative capacity is associated with a decline of effectiveness in stem cell fusion. We project how studies into the fusion of stem cells with tissue cells, or the fusion between activator stem cells and patient cells might help in the development of applications that "rejuvenate" certain target cells, thereby strategically reinstating a regeneration cascade. The outlook is concluded with a discussion of the next research milestones and the potential hazards of fusion therapies.

Sturm, A., et al. (2017). "The Piwi-piRNA pathway: road to immortality." Aging Cell 16(5): 906-911.

Despite its medical, social, and economic significance, understanding what primarily causes aging, that is, the mechanisms of the aging process, remains a fundamental and fascinating problem in biology. Accumulating evidence indicates that a small RNA-based gene regulatory machinery, the Piwi-piRNA pathway, represents a shared feature of nonaging (potentially immortal) biological systems, including the germline, somatic cancer stem cells, and certain 'lower' eukaryotic organisms like the planarian flatworm and freshwater hydra. The pathway primarily functions to repress the activity of mobile genetic elements, also called transposable elements (TEs) or 'jumping genes', which are capable of moving from one genomic locus to another, thereby causing insertional mutations. TEs become increasingly active and multiply in the genomes of somatic cells as the organism ages. These characteristics of TEs highlight their decisive mutagenic role in the progressive disintegration of genetic information, a molecular hallmark associated with aging. Hence, TE-mediated genomic instability may substantially contribute to the aging process.

Svendsen, J. M., et al. (2019). "henn-1/HEN1 Promotes Germline Immortality in Caenorhabditis elegans." Cell Rep 29(10): 3187-3199 e3184.

The germline contains an immortal cell lineage that ensures the faithful transmission of genetic and, in some instances, epigenetic information from one generation to the next. Here, we show that in Caenorhabditis elegans, the small RNA 3'-2'-O-methyltransferase henn-1/HEN1 is required for sustained fertility across generations. In the absence of henn-1, animals become progressively less fertile, becoming sterile after approximately 30 generations at 25 degrees C. Sterility in henn-1 mutants is accompanied by severe defects in germline proliferation and maintenance. The requirement for henn-1 in transgenerational fertility is likely due to its role in methylating and, thereby, stabilizing Piwi-interacting RNAs (piRNAs). However, despite being essential for piRNA stability in embryos, henn-1 is not required for piRNA stability in adults. Thus, we propose that methylation is important for the role of piRNAs in establishing proper gene silencing during early stages of development but is dispensable for their role in the proliferated germline.

Szawarski, P. (2018). "Classic cases revisited: Mr Miura and the delusion of immortality." J Intensive Care Soc 19(3): 269-273.

Death continues to be viewed as a failure by many clinicians and society. For now however, it remains a biological certainty and to think otherwise is to delude oneself. Nevertheless, the society is becoming older and many individuals enjoy fulfilling life in spite of advancing years. The trajectory of age-related physiological deterioration varies, introducing an uncertainty as to the potential for survival when faced with critical illness. There is risk of harm associated with invasive interventions and utility of such remains uncertain in the very elderly. Changing demographic demands improved triage of the elderly patients and an evolution of the research agenda to acknowledge ageing population. There is also moral imperative to ensure avoidance of harm and cost-effectiveness in relation to intensive care unit utilisation by this patient population.

Takasaki, T., et al. (2007). "MRG-1, an autosome-associated protein, silences X-linked genes and protects germline immortality in Caenorhabditis elegans." Development 134(4): 757-767.

MRG15, a mammalian protein related to the mortality factor MORF4, is required for cell proliferation and embryo survival. Our genetic analysis has revealed that the Caenorhabditis elegans ortholog MRG-1 serves similar roles. Maternal MRG-1

promotes embryo survival and is required for proliferation and immortality of the primordial germ cells (PGCs). As expected of a chromodomain protein, MRG-1 associates with chromatin. Unexpectedly, it is concentrated on the autosomes and not detectable on the X chromosomes. This association is not dependent on the autosome-enriched protein MES-4. Focusing on possible roles of MRG-1 in regulating gene expression, we determined that MRG-1 is required to maintain repression in the maternal germ line of transgenes on extrachromosomal arrays, and of several X-linked genes previously shown to depend on MES-4 for repression. MRG-1 is not required for PGCs to acquire transcriptional competence or for the turn-on of expression of several PGC-expressed genes (pgl-1, glh-1, glh-4 and nos-1). By contrast to this result in PGCs, MRG-1 is required for ectopic expression of those germline genes in somatic cells lacking the NuRD complex component MEP-1. We discuss how an autosome-enriched protein might repress genes on the X chromosome, promote PGC proliferation and survival, and influence the germ versus soma distinction.

Torres-Padilla, M. E. and R. Ciosk (2013). "A germline-centric view of cell fate commitment, reprogramming and immortality." Development 140(3): 487-491.

To ensure species continuity, the tantalising developmental plasticity of early embryonic cells, also called totipotency, must be transmitted to the offspring. This responsibility rests within the reproductive cell lineage: the germ line. At the recent EMBO/EMBL symposium 'Germline - Immortality through Totipotency', researchers discussed the mechanisms that establish and control totipotency, with an eye towards the mechanisms that may endow germ cells with the ability to propagate totipotency across generations.

Tousian, H., et al. (2020). "Looking for immortality: Review of phytotherapy for stem cell senescence." Iran J Basic Med Sci 23(2): 154-166.

In this paper, we discussed natural agents with protective effects against stem cell senescence. Different complications have been observed due to stem cell senescence and the most important of them is "Aging". Senescent cells have not normal function and their secretary inflammatory factors induce chronic inflammation in body which causes different pathologies. Stem cell senescence also has been investigated in different diseases or as drug adverse effects. We searched databases such as Embase, Pubmed and Web of Science with keywords "stem cell", "progenitor cell", "satellite", "senescence" and excluded keywords "cancer", "tumor", "malignancy" and "carcinoma" without time limitation until May 2019. Among them we chose 52 articles that have investigated protective effects of natural agents (extracts or molecules) against cellular senescence in different kind of adult stem cells. Most of these studies were in endothelial progenitor cells, hematopoietic stem cells, mesenchymal stem cells, adipose-derived stem cells and few were about other kinds of stem cells. Most studied agents were resveratrol and ginseng which are also commercially available as supplement. Most protective molecular targets were telomerase and anti-oxidant enzymes to preserve genome integrity and reduce senescence-inducing signals. Due to the safe and long history of herbal usage in clinic, phytotherapy can be used for preventing stem cell senescence and their related complication. Resveratrol and ginseng can be the first choice for this aim due to their protective mechanisms in various kinds of stem cells and their long term clinical usage.

Trent, B. (2004). "The future of immortality." Humanist 64(3): 11-15.

Trent shares his perspectives on the mechanics of future immortality and death, which are being laid bare in laboratories around the world. He reiterates that even among new immortals, there will likely be people who, after a full life of two hundred or two million years, will decide that enough is simply enough, and that death may be as optional as the hair dye.

Trentesaux, C. and J. F. Riou (2010). "[Senescence and cellular immortality]." Bull Cancer 97(11): 1275-1283.

Senescence was originally described from the observation of the limited ability of normal cells to grow in culture, and may be generated by telomere erosion, accumulation of DNA damages, oxidative stress and modulation of oncogenes or tumor suppressor genes. Senescence corresponds to a cellular response aiming to control tumor progression by limiting cell proliferation and thus constitutes an anticancer barrier. Senescence is observed in pre-malignant tumor stages and disappears from malignant tumors. Agents used in standard chemotherapy also have the potential to induce senescence, which may partly explain their therapeutic activities. It is possible to restore senescence in tumors using targeted therapies that triggers telomere dysfunction or reactivates suppressor genes functions, which are essential for the onset of senescence.

Urban, M. (1998). "Lack of evidence for dominant mortality alleles at the divine immortality (DIM) locus." Am J Med Genet 78(5): 485-486.

Vail, K. E., 3rd, et al. (2020). "Natural, But Not Supernatural, Literal Immortality Affirmation Attenuates Mortality Salience Effects on Worldview Defense in Atheists." Pers Soc Psychol Bull 46(2): 312-326.

The present research explored whether atheists managing death awareness would be effectively buffered by affirmations of supernatural

and/or natural literal immortality. Prior data were reanalyzed, revealing ambiguous results, so further experiments were conducted. In Study 1 (n = 382), atheists were randomly assigned to a supernatural afterlife-confirmed (vs. afterlife-disconfirmed) prime, an MS (vs. control topic) prime, and then given an opportunity to engage in secular worldview defense. In Study 2 (n = 360), atheists were randomly assigned to supernatural (afterlife) versus natural (medical indefinite life extension; MILE) immortality prime, an MS (vs. control topic) prime, and then given an opportunity to engage in secular worldview defense. Atheists managing death awareness increased worldview defense in the supernatural/afterlife conditions but that effect was eliminated in the MILE condition. These findings are consistent with the terror management theory perspective on worldview defense. Implications for theory and research are discussed.

Vidal, C. (2014). "Cosmological immortality: how to eliminate aging on a universal scale." Curr Aging Sci 7(1): 3-8.

The death of our universe is as certain as our individual death. Some cosmologists have elaborated models which would make the cosmos immortal. In this paper, I examine them as cosmological extrapolations of immortality narratives that civilizations have developed to face death anxiety. I first show why cosmological death should be a worry, then I briefly examine scenarios involving the notion of soul or resurrection on a cosmological scale. I discuss in how far an intelligent civilization could stay alive by engaging in stellar, galactic and universal rejuvenation. Finally, I argue that leaving a cosmological legacy via universe making is an inspiring and promising narrative to achieve cosmological immortality.

Wadhwa, R., et al. (1991). "Protein markers for cellular mortality and immortality." Mutat Res 256(2-6): 243-254.

Fixed mortality of normal somatic cells is a well-established fact though the mechanism underlying this universal phenomenon remains unknown. Use of immortal cells in conjunction with their normal mortal counterparts has delineated the dominant genetic nature of the senescent phenotype over immortalization. Although the involvement of proteins in determining the entry/exit/arrest of cells in the cell cycle is evident from the literature, none of them has been confirmed for its role in senescence-associated irreversible cell cycle exit/arrest. The identification of true mortality markers might be possible by selecting a system of natural and conditional aging achieved by the fusion of mortal and spontaneously immortalized cells of the same origin. We report here a few such protein markers which might serve as useful handles to tease out the molecular events determining mortality/immortality of cultured cells.

Wadhwa, R., et al. (1995). "Correlation between complementation group for immortality and the cellular distribution of mortalin." Exp Cell Res 216(1): 101-106.

The dominance of cellular senescence over the immortal phenotype has been demonstrated by cell fusion experiments utilizing human and mouse cells. Mortalin, a novel 66-kDa member of the murine hsp70 family of proteins, has recently been identified as a marker of the mortal phenotype by virtue of its characteristic cytosolic distribution in mortal cells. Here we report the mortalin immunostaining observations on 21 human cell lines. These cell lines have previously been assigned by somatic cell hybridization analysis to one (18 lines) or more than one (3 lines) of the four complementation groups (A, B, C, and D) for immortalization. Four patterns of mortalin immunostaining were observed: granular-juxtanuclear cap, granular-gradient from nuclear to cell membrane, granular-juxtanuclear arch, and fibrous-perinuclear. In 17 of 18 cell lines assigned to a single complementation group, the mortalin staining corresponded with the complementation group. In two of the three cell lines previously assigned to multiple complementation groups, the mortalin staining corresponded to one of the assigned groups. Two cell lines, however, exhibited staining patterns which did not match to their assigned complementation groups. The basis of correlation between cellular distribution of mortalin and the complementation group remains unclear at present. However, the data (i) suggest that the intracellular distribution of mortalin can be used to distinguish mortal and immortal cells, confirming the association of mortalin with senescence; (ii) provide supportive evidence for the existence of at least four different pathways of immortalization in human cells; and (iii) indicate that mortalin is involved in processes that result in immortalization.

Walen, K. H. and M. R. Stampfer (1989). "Chromosome analyses of human mammary epithelial cells at stages of chemical-induced transformation progression to immortality." Cancer Genet Cytogenet 37(2): 249-261.

Benzo(a)pyrene induced extended life (EL) (i.e., a longer than normal proliferative lifespan before senescence) of human breast cells in culture. From many EL cell cultures immortalized cells emerged only once in each of two separate experiments. The original EL cells were mostly normal diploid with only a small percentage of tetraploid cells. The two immortalized cell lines, however, were near diploid, each containing a set of chromosomal aberrations that were present in all the cells analyzed, confirming the clonal origin of both cell lines. For cell line 184A1 the aberrations consisted of deficiencies only, whereas a combination of deficiencies and duplications characterized the 184B5 line. None of the individual aberrations of each

set were shared by both cell lines. Both sets of aberrations have remained stable for over 150 population doublings, while some of the other chromosomes showed breakage and reunions. These data are discussed in regard to types of mutations in the sequence of changes from primary to immortalized cells, and it is concluded that the sets of aberrations most likely originated as multiple events in a single cell.

Wan, G., et al. (2021). "ZSP-1 is a Z granule surface protein required for Z granule fluidity and germline immortality in Caenorhabditis elegans." EMBO J 40(3): e105612.

Germ granules are biomolecular condensates that form in germ cells of all/most animals, where they regulate mRNA expression to promote germ cell function and totipotency. In the adult Caenorhabditis elegans germ cell, these granules are composed of at least four distinct sub-compartments, one of which is the Z granule. To better understand the role of the Z granule in germ cell biology, we conducted a genetic screen for genes specifically required for Z granule assembly or morphology. Here, we show that zsp-1, which encodes a low-complexity/polyampholyte-domain protein, is required for Z granule homeostasis. ZSP-1 localizes to the outer surface of Z granules. In the absence of ZSP-1, Z granules swell to an abnormal size, fail to segregate with germline blastomeres during development, and lose their liquid-like character. Finally, ZSP-1 promotes piRNA- and siRNA-directed gene regulation and germline immortality. Our data suggest that Z granules coordinate small RNA-based gene regulation to promote germ cell function and that ZSP-1 helps/is need to maintain Z granule morphology and liquidity.

Watanabe, H., et al. (2009). "Immortality and the base of multicellular life: Lessons from cnidarian stem cells." Semin Cell Dev Biol 20(9): 1114-1125.

Cnidarians are phylogenetically basal members of the animal kingdom (>600 million years old). Together with plants they share some remarkable features that cannot be found in higher animals. Cnidarians and plants exhibit an almost unlimited regeneration capacity and immortality. Immortality can be ascribed to the asexual mode of reproduction that requires cells with an unlimited self-renewal capacity. We propose that the basic properties of animal stem cells are tightly linked to this archaic mode of reproduction. The cnidarian stem cells can give rise to a number of differentiated cell types including neuronal and germ cells. The genomes of Hydra and Nematostella, representatives of two major cnidarian classes indicate a surprising complexity of both genomes, which is in the range of vertebrates. Recent work indicates that highly conserved signalling pathways control Hydra stem cell differentiation. Furthermore, the availability of genomic resources and novel technologies provide approaches to analyse these cells in vivo. Studies of stem cells in cnidarians will therefore open important insights into the basic mechanisms of stem cell biology. Their critical phylogenetic position at the base of the metazoan branch in the tree of life makes them an important link in unravelling the common mechanisms of stem cell biology between animals and plants.

Watanabe, N. (2001). "[Telomerase, cell immortality and cancer]." Hokkaido Igaku Zasshi 76(3): 127-132.

Telomerase is an enzyme that replaces repetitive (TTAGGG)n sequences on the ends of chromosomes that would otherwise be lost during successive cell divisions. Telomerase activity is closely linked to attainment of cellular immortality, a step in carcinogenesis, while lack of such activity contributes to cellular senescence. Telomerase is activated in more than 85% of malignant tumors. However, with the exception of some self-renewing tissues with high regenerative potential, telomerase activity is usually repressed in normal somatic tissues. Based on these reports, we investigated telomerase activity in gastric mucosal tissues. Telomerase activity is highest in cancer, followed by intestinal metaplasia, chronic gastritis, and normal mucosa. In patients with intestinal-type gastric cancer, telomerase activity was higher in those with intestinal metaplasia and H. pylori infection than in patients without infection. Our results suggest that H. pylori infection may influence telomerase activity in cancer and noncancerous tissue. Genes encoding three major components of human telomerase have been recently cloned. They included those for human telomerase RNA component (hTR), human telomerase reverse transcriptase (hTERT), and telomerase-associated protein 1 (TEP1). More recently, two human telomeric repeat binding factors (TRFs) have also been cloned: TRF1, considered to inhibit the action of telomerase at the telomeric region, and TRF2, believed to prevent fusion of chromosome ends and, in vitro, to remodel linear telomeric DNA into large duplex loops. However, the details of mechanisms regulating telomerase activity are still poorly understood, and specific components or binding proteins that might represent suitable targets for cancer gene therapy have not yet been identified. Therefore, we established quantitative assays using a TaqMan RT-PCR for mRNAs encoding the telomerase components hTR, hTERT, and TEP1, as well as for those encoding TRF1 and TRF2. By using our quantitative assays, we found the following results: 1) Expression of TRF1 and TRF2 mRNA was greater in the normal cells than in human malignant hematopoietic cell lines or in patients with acute leukemia, 2) hTERT mRNA expression showed changes paralleling telomerase activity and became undetectable with HL60 cell differentiation, 3) initially low expression of TRF1 and TRF2 mRNA

increased during differentiation. Our results suggest that not only hTERT but also TRF1 and 2 are important regulators of telomerase activity.

Wisman, A. and N. A. Heflick (2016). "Hopelessly mortal: The role of mortality salience, immortality and trait self-esteem in personal hope." Cogn Emot 30(5): 868-889.

Do people lose hope when thinking about death? Based on Terror Management Theory, we predicted that thoughts of death (i.e., mortality salience) would reduce personal hope for people low, but not high, in self-esteem, and that this reduction in hope would be ameliorated by promises of immortality. In Studies 1 and 2, mortality salience reduced personal hope for people low in self-esteem, but not for people high in self-esteem. In Study 3, mortality salience reduced hope for people low in self-esteem when they read an argument that there is no afterlife, but not when they read "evidence" supporting life after death. In Study 4, this effect was replicated with an essay affirming scientific medical advances that promise immortality. Together, these findings uniquely demonstrate that thoughts of mortality interact with trait self-esteem to cause changes in personal hope, and that literal immortality beliefs can aid psychological adjustment when thinking about death. Implications for understanding personal hope, trait self-esteem, afterlife beliefs and terror management are discussed.

Wong, K. S., et al. (1999). "Loss of p53 in F-MuLV induced-erythroleukemias accelerates the acquisition of mutational events that confers immortality and growth factor independence." Oncogene 18(40): 5525-5534.

Erythroleukemias induced by Friend Murine Leukemia Virus (F-MuLV) involve the insertional activation of the proto-oncogene Fli-1, and the inactivation of the p53 tumor suppressor gene. While the activation of Fli-1 is an early, primary transforming event, p53 mutations are correlated with the immortalization of erythroleukemic cells in culture. In this study we have further analysed the role of p53 loss in F-MuLV induced erythroleukemias by examining the progression of this disease in p53 deficient mice. We found that p53-/- mice succumb to the disease more rapidly than p53+/+ littermates. Additionally, of the 112 tumors generated, 19 gave rise to immortal cell lines, eight of which were derived from p53-/- mice, and ten of which were from p53+/- mice. The ability of these primary tumor cells to grow in culture was associated with the complete loss of wild-type p53 in these cell lines. However, cells from many of the tumors induced in p53-/- hosts did not survive in vitro. These results suggest that the loss of p53 does not directly immortalize tumor cells. Instead, we have evidence to suggest that the loss of p53 promotes the accumulation of mutations that are required for survival in culture and that are capable of accelerating tumor progression in vivo. Indeed, mutations causing expression of the growth factor gene erythropoietin (Epo), were detected in two of seven Epo-independent cell lines from p53 deficient primary erythroleukemias. Moreover, the mechanism of activation of the Epo gene in one of these two Epo-independent cell lines involved genomic rearrangement, that is a hallmark of genetic instability. We propose that, in F-MuLV induced-erythroleukemias, p53 loss may encourage the accumulation of further mutations, subsequently conferring a growth advantage and immortality to the transformed erythroblasts.

Wynford-Thomas, D., et al. (1989). "Suppression of transformation and immortality in human/Chinese hamster fibroblast hybrids--a model for suppressor gene isolation." Int J Cancer 43(2): 293-299.

Somatic cell hybrids were produced by fusion of normal human (foreskin) fibroblasts and a transformed Chinese hamster fibroblast line V79-8. Overall, approximately 30% of hybrid clones showed stable reversion to normal morphology and growth control in vitro as shown by serum and anchorage dependence. In one-third of these clones, senescence was observed after a number of generations similar to that required for the human fibroblast parent cells to senesce. The remainder appear to be immortal. Normal human chromosomes can therefore restore growth control with or without finite life-span to this transformed cell. V79 cells were found to be transfectable at an efficiency compatible with detection of single-copy gene transfer from genomic DNA. Furthermore, these cells were exceptionally sensitive to negative ("suicide") selection. Taken together, our data suggest that the V79 line represents an ideal system for isolation of human tumour suppressor genes.

Yamamoto, I., et al. (2021). "Telomeric double-strand DNA-binding proteins DTN-1 and DTN-2 ensure germline immortality in Caenorhabditis elegans." Elife 10.

Telomeres are nucleoprotein complexes at the ends of chromosomes and are indispensable for the protection and lengthening of terminal DNA. Despite the evolutionarily conserved roles of telomeres, the telomeric double-strand DNA (dsDNA)-binding proteins have evolved rapidly. Here, we identified double-strand telomeric DNA-binding proteins (DTN-1 and DTN-2) in Caenorhabditis elegans as non-canonical telomeric dsDNA-binding proteins. DTN-1 and DTN-2 are paralogous proteins that have three putative MYB-like DNA-binding domains and bind to telomeric dsDNA in a sequence-specific manner. DTN-1 and DTN-2 form complexes with the single-strand telomeric DNA-binding proteins POT-1 and POT-2 and constitutively localize to telomeres. The dtn-1 and dtn-2 genes function redundantly, and their simultaneous

deletion results in progressive germline mortality, which accompanies telomere hyper-elongation and chromosomal bridges. Our study suggests that DTN-1 and DTN-2 are core shelterin components in C. elegans telomeres that act as negative regulators of telomere length and are essential for germline immortality.

Yamamoto, T., et al. (2017). "Cell physiology of mortality and immortality in a Nicotiana interspecific F1 hybrid complies with the quantitative balance between reactive oxygen and nitric oxide." J Plant Physiol 210: 72-83.

The cultured cell line, GTH4, of an interspecific F1 hybrid between Nicotiana gossei Domin and N. tabacum L. died after a shift in temperature from 37 degrees C to 26 degrees C. Fluctuations in the cellular amounts of reactive oxygen species (ROS) and nitric oxide (NO) were detected in GTH4 after the temperature shift, but not in the mutant, GTH4S, which did not die at 26 degrees C presumably due to the lack of genetic factors involved in cell death. The removal of ROS or NO suppressed cell death in GTH4, suggesting that ROS and NO both acted as mediators of cell death. However, excess amounts of the superoxide anion (O2(-)) or NO alleviated cell death. A series of experiments using generators and scavengers of ROS and NO showed that O2(-) affected the cellular levels of NO, and vice versa, indicating that a quantitative balance between O2(-) and NO was important for hybrid cell death. The combination of NO and hydrogen peroxide (H2O2) was necessary and sufficient to initiate cell death in GTH4 and GTH4S. Hypoxia, which suppressed cell death in GTH4 at 26 degrees C, reduced the generation of H2O2 and NO, but allowed for the production of O2(-), which acted as a suppressor and/or modulator of cell death. The activation of MAPK was involved in the generation of H2O2 in GTG4 cells under normoxic conditions, but promoted O2(-) generation under hypoxic conditions. More protective cellular conditions against ROS, as estimated by the expression levels of genes for ROS-scavenging enzymes, may be involved in the mechanisms responsible for the low cell death rate of GTH4 under hypoxic conditions.

Yaswen, P., et al. (2015). "Therapeutic targeting of replicative immortality." Semin Cancer Biol 35 Suppl: S104-S128.

One of the hallmarks of malignant cell populations is the ability to undergo continuous proliferation. This property allows clonal lineages to acquire sequential aberrations that can fuel increasingly autonomous growth, invasiveness, and therapeutic resistance. Innate cellular mechanisms have evolved to regulate replicative potential as a hedge against malignant progression. When activated in the absence of normal terminal differentiation cues, these mechanisms can result in a state of persistent cytostasis. This state, termed "senescence," can be triggered by intrinsic cellular processes such as telomere dysfunction and oncogene expression, and by exogenous factors such as DNA damaging agents or oxidative environments. Despite differences in upstream signaling, senescence often involves convergent interdependent activation of tumor suppressors p53 and p16/pRB, but can be induced, albeit with reduced sensitivity, when these suppressors are compromised. Doses of conventional genotoxic drugs required to achieve cancer cell senescence are often much lower than doses required to achieve outright cell death. Additional therapies, such as those targeting cyclin dependent kinases or components of the PI3K signaling pathway, may induce senescence specifically in cancer cells by circumventing defects in tumor suppressor pathways or exploiting cancer cells' heightened requirements for telomerase. Such treatments sufficient to induce cancer cell senescence could provide increased patient survival with fewer and less severe side effects than conventional cytotoxic regimens. This positive aspect is countered by important caveats regarding senescence reversibility, genomic instability, and paracrine effects that may increase heterogeneity and adaptive resistance of surviving cancer cells. Nevertheless, agents that effectively disrupt replicative immortality will likely be valuable components of new combinatorial approaches to cancer therapy.

Yildiz, G., et al. (2013). "Genome-wide transcriptional reorganization associated with senescence-to-immortality switch during human hepatocellular carcinogenesis." PLoS One 8(5): e64016.

Senescence is a permanent proliferation arrest in response to cell stress such as DNA damage. It contributes strongly to tissue aging and serves as a major barrier against tumor development. Most tumor cells are believed to bypass the senescence barrier (become "immortal") by inactivating growth control genes such as TP53 and CDKN2A. They also reactivate telomerase reverse transcriptase. Senescence-to-immortality transition is accompanied by major phenotypic and biochemical changes mediated by genome-wide transcriptional modifications. This appears to happen during hepatocellular carcinoma (HCC) development in patients with liver cirrhosis, however, the accompanying transcriptional changes are virtually unknown. We investigated genome-wide transcriptional changes related to the senescence-to-immortality switch during hepatocellular carcinogenesis. Initially, we performed transcriptome analysis of senescent and immortal clones of Huh7 HCC cell line, and identified genes with significant differential expression to establish a senescence-related gene list. Through the analysis of senescence-related gene expression in

different liver tissues we showed that cirrhosis and HCC display expression patterns compatible with senescent and immortal phenotypes, respectively; dysplasia being a transitional state. Gene set enrichment analysis revealed that cirrhosis/senescence-associated genes were preferentially expressed in non-tumor tissues, less malignant tumors, and differentiated or senescent cells. In contrast, HCC/immortality genes were up-regulated in tumor tissues, or more malignant tumors and progenitor cells. In HCC tumors and immortal cells genes involved in DNA repair, cell cycle, telomere extension and branched chain amino acid metabolism were up-regulated, whereas genes involved in cell signaling, as well as in drug, lipid, retinoid and glycolytic metabolism were down-regulated. Based on these distinctive gene expression features we developed a 15-gene hepatocellular immortality signature test that discriminated HCC from cirrhosis with high accuracy. Our findings demonstrate that senescence bypass plays a central role in hepatocellular carcinogenesis engendering systematic changes in the transcription of genes regulating DNA repair, proliferation, differentiation and metabolism.

Zhou, Y., et al. (2013). "Stem cells' exodus: a journey to immortality." Dev Cell 24(2): 113-114.

Stem cell niches provide a regulatory microenvironment that retains stem cells and promotes self-renewal. Recently in Developmental Cell, Rinkevich et al. (2013) showed that cell islands (CIs) of Botryllus schlosseri, a colonial chordate, provide niches for maintaining cycling stem cells that migrate from degenerated CIs to newly formed buds.

Zhu, X., et al. (2010). "The intrabody targeting of hTERT attenuates the immortality of cancer cells." Cell Mol Biol Lett 15(1): 32-45.

hTERT (human telomerase reverse transcriptase) plays a key role in the process of cell immortalization. Overexpression of hTERT has been implicated in 85% of malignant tumors and offers a specific target for cancer therapy. In this paper, we describe an effective approach using a single-chain variable fragment (scFv) intrabody derived from monoclonal hybridoma directed against hTERT to attenuate the immortalization of human uterine cervix and hepatoma cells. The scFv we constructed had a high affinity to hTERT, and specifically neutralized over 70% of telomere synthesis activity, thereby inhibiting the viability and proliferation of the cancer cells. Our results indicate that this anti-hTERT intrabody is a promising tool to target hTERT and intervene in the immortalization process of cancer cells.

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