Open Access Library Journal
2025, Volume 12, e13617
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Plastic Surgery Update on Epigenetic Reprogramming of Aging (ERA): Mechanisms, Pathways and Strategies toward Cell-Free Aesthetic Rejuvenating Applications

Gordon Hiroshi Sasaki[1,2]

[1]Sasaki Advanced Aesthetic Medical Center, Pasadena, USA
[2]Loma Linda University Medical Center, Loma Linda, USA
Email: ghsasakimd@drsasaki.com

How to cite this paper: Sasaki, G.H. (2025) Plastic Surgery Update on Epigenetic Reprogramming of Aging (ERA): Mechanisms, Pathways and Strategies toward Cell-Free Aesthetic Rejuvenating Applications. *Open Access Library Journal*, **12**: e13617.
https://doi.org/10.4236/oalib.1113617

Received: May 16, 2025
Accepted: July 12, 2025
Published: July 15, 2025

Abstract

Epigenetics can be defined as a heritable or reversible change in gene expression that is not accompanied by changes in DNA sequences. Epigenetics provides an additional layer of instructions that can affect where and when genes are expressed, modulating the aging process in response to an array of environmental factors such as diet, lifestyle, genetics and disease. Subsequent changes at the gene level are likely to contribute to cell, organ and body senescence affecting the health and well-being of patients. In recent years, regenerative aesthetic medicine has been integrated in the management of aging skin to either replace or restore damaged and dysfunctional skin cells to acquire more youthful appearance and function. In the past decade, small molecule-based pre-clinical studies are investigating partial epigenetic reprogramming intervention strategies for epigenetic rejuvenation to reduce or reverse these infirmities through modifications of epigenetic marks and gene expression patterns.

Subject Areas

Surgery & Surgical Specialties

Keywords

Partial Epigenetic Reprogramming, Skin Rejuvenation, Aging Skin

1. Introduction

In recent years, regenerative medicine has become an integral part of plastic sur-

gery because of similar goals to restore old, damaged and dysfunctional cells in tissues to nearly their original functional and structural state and rejuvenate them expectedly to acquire younger characteristics that may lead to aesthetic changes in tissue appearance. Aging cells share certain molecular characteristics and defective manifestations of genetic and environmental changes that include epigenetic alterations, senescence, telomere attrition, genomic instability, stem cell exhaustion, deregulated nutrient-sensing, loss of proteostasis, mitochondrial dysfunction, altered intercellular communication, disabled macro-autophagy, chronic inflammation, and dysbiosis [1]. These twelve revelations, collectively regarded as the "expanded hallmarks of aging", are inherently linked in their actions and produce quantifiable and overlapping signs of cellular decline affected by both chronological and biological factors. Accentuation or attenuation of one hallmark is not an isolated event and usually affects the structure and functions of others.

Among the twelve hallmarks of aging, epigenetic modifications are considered one of the critical determinants of cellular and tissue aging that often preceded and impacted other aspects of age-related degeneration [2]-[4]. Clearly, aging is associated with the accumulation of DNA damage and mutations, as well as telomere shortening, but there is an increasing body of evidence that aging might also be due to epigenetics [3] [6]. Modification of epigenetic factors are believed to serve in a regulatory capacity between environmental cues and enactment of genomic signals and thus have the unique ability to produce different observable phenotypic traits from a single genotype. Triggering of these epigenetic processes is believed to alter adversely gene expression thereby initiating down-stream transcriptional events of cellular cells deterioration, aging, and loss of their vital functions over time [6]. These age-associated epigenetic elements are associated, but not limited, to DNA methylation (DNAm), histone modification, chromatin remodeling, non-coding RNA (ncRNA) regulation, and RNA modification. To understand the interactive actions of epigenetic factors and their consequences on cellular aging, a basic review of chromatin, epigenetics, epigenetic-clock and drift, and reprogramming strategies is presented. A significant number of scholarly articles [3] [7]-[10] are recommended to clarify the achievements and reservations in the field of genetics, genomics, and epigenetics that participate in the interactions between genes and the environment's role in affecting them.

2. Chromatin and Nuclear Architecture

DNA chains within chromosomes are subjected to continual alterations and destruction that may deregulate cellular identity and function. To manage these daily normal assignments against assaults, long strands of nuclear DNA are tightly coiled around spools of proteins, called histones, within complex packets known as chromatin [11]. Histones are comprised of two sets of four protein cores dimers (Histone H2A, Histone H2B, Histone H3, and Histone H4), containing high proportion of basic amino acids (arginine and lysine), that enable tight binding, anchoring, and packing of negatively charged DNA molecules into small compo-

nents called nucleosomes. The more densely the nucleosomes are arranged around histones, the more protected the DNA is from damage [12], but provides less spacing for transcription of RNAs and post-transitional proteins and suppresses gene expression [13]. About 10 percent of genes in the human genome encode DNA-binding proteins, like histones, that can attach to specific sites on DNA to activate or suppress gene expression. The level of chromatin nucleosome compactness is manipulated either to support a relatively stable nuclear architecture for proper genetic actions and their post-transitional protein production or to cause the nuclear architecture to exhibit instability through environmental modifications of DNA or of histones that may result in cellular aging and disease. The current goals of genomics, genetics and epigenetic studies are focused on identifying and characterizing the functions of genetic alterations and epigenetic changes that contribute to cancerous development and growth, developing newer sophisticated analytic methods, and development of alternative therapies that take advantage of the genetic and epigenetic influences in cancer. More recently, attention has targeted identifying characteristics within aging cellular tissues and exploiting them to partially reverse them through epigenetic reprogramming for more youthful modifications of functions and appearances.

3. Epigenetics

Epigenetics can be defined as a heritable or reversible change in gene expression that is not accompanied by changes in DNA sequences. The word "epigenetics' is derived from the Greek word "epi", meaning "over" or "above," and in this case, over and above the genome. Epigenetics provides an additional layer of instructions that can affect where and when genes are expressed, modulating the aging process in response to an array of environmental factors such as diet, lifestyle, genetics and disease.

DNA methylation, a prominent epigenetic mark, is considered a major epigenetic modifier that has profound effects on gene expression by attaching methyl groups to cytosine/guanine dinucleotides (CpG islands) on the histones, reducing spacing and organization of genes. This effect can turn "off" specific genomic messaging so that they do not read. Histones are often referred to as the epigenome ("over" the genome) and consist of "marks," which are not part of the DNA itself but can be passed on from cell-to-cell. About 60% of human genes contain about 29,000 CpG islands. Through a "Histone Code," post-translational modifications are believed to regulate the complex expression of genes between histones and genes during periods of epigenetic chromatin silentness [13]-[16]. The molecular mechanisms of epigenetic silencing remain incompletely understood but is believed to involve the processes not only of methylation but also phosphorylation, acetylation, ubiquitylation, and ADP-ribosylation with histone proteins, DNA and RNA [3].

3.1. Chronological versus Epigenetic Biologic Aging

Chronological aging is a measure of the number of years a person has lived from

date of birth [17]. In contrast, an individual's biological age is a proxy for an individual's overall physiological and health status that can display a faster or slower aging, in relation to his/her chronological age. An ideal biological age estimator correlates not only with chronological age but also with additional epigenetic information on an individual's risk for age-related conditions. Numerous physiological, functional, cellular and molecular features have been proposed as epigenetic biological age predictors, but few have been robust or precise.

3.2. Epigenetic Clocks

For over fifty years, sets of CpGs-DNA methylation (DNAm) levels have been strongly correlated with cellular aging [18]-[22] although other candidate markers have been identified such as telomere length, transcriptomics, proteomics, metabolomics, and composite biomarker panels [1] [23]-[25]. Bocklandt and his group [26] published the first study in 2011 that demonstrated DNAm levels in saliva could accurately predict average biological age. A few years later, Hannum's whole blood epigenetic clock of 71 markers precisely estimated age from blood methylation levels [27]. In 2013, the first multi-tissue epigenetic clock of 353 CpGs by Horvath and his team [28] compared ages from highly predictive data sets of different tissues and cell types with the same algorithm irrespective of DNA source. Besides the verified Hannum-Horvath models [29], second-generation epigenetic clocks, such as DNA PhenoAge [23] and DNA GrimAge [30] have been developed based on correlation between methylation and health risks scores. Recently, Belsky *et al.* [31] developed the Dunedin Pace of Aging Methylation, the third-generation Epigenetic Age Acceleration clock, that defined differences measured between greater biological age and chronological age related to consequence of low physical activity, obesity, alcohol, and smoking abuse [32]-[34]. The excitement following the development of epigenetic clocks has been tempered as to the meaning of their measurements as each clock uses a different calibration of tissue type, sample size, and statistical approach [35]. This uncertainty is compounded by the fact that different epigenetic clocks appear to measure different features of aging. Studies have suggested that epigenetic aging is associated with nutrient sensing [36], mitochondrial activity [37], stem cell exhaustion [38], but distinct from cellular senescence [39], telomere attrition [40], and genomic instability [41]. The absence of a connection between the other aging landmarks and epigenetic aging suggests that aging is a consequence of multi-parallel mechanisms of deterministic pathways. Despite these discrepancies, epigenetic clocks will continue to bring even greater clarity to the overall process of aging and chronic diseases. Current epigenetic clocks are being explored for their potential to predict and reverse skin aging. Although research in first and third generation clocks demonstrates promising results to assess large groups, limitations exist in predicting individual skin aging rates. Some studies have developed clocks specifically for skin, like "VisAgeX" clock, which is believed to accurately predict skin age progression with a focus on identifying key biological pathways associated with skin aging [42].

Boroni [43] developed an accurate skin age predictor using 2266 CpG sites and DNA methylation pattern's to assess the impact of various factors on aging skin, including UV exposure, pollution, and the efficacy of anti-aging senotherapeutic treatments. This "MolClock" provides one of the more comprehensive and highly accurate methods to analyze human skin health status and aging. Further longitudinal cohort studies are needed to better understand how epigenetic clocks measure relationships between skin biological aging and chronological aging based on epigenetic skin changes, facial visual aging skin signs, proteosome signatures, inflammatory and immune pathways, biophysical skin changes, and biopsies.

In contrast to aforementioned epigenetic clocks that estimate chronological/biological aging, epigenetic drift refers to a random process of both gains and losses of the methylation state of CpG and nucleotide composition of adjacent sequences over time [44]. Epigenetic drift occurs when the original methylation states of CpG dinucleotides are altered as a result of random errors from the imperfect fidelity of DNA methyltransferase (DNMT) enzymes that copy DNAm patterns from parental DNA during faulty DNA repair [45]. Gains of CpG methylation during drifts may become likely markers of cell divisions or cell turnovers that may be useful in timing the initiation and progression of cancers [46]. In summary, understanding epigenetic aging mechanisms may provide strategies to delay aging and treatment of diseases [9].

4. Epigenetic Reprogramming

Cellular, tissue, and organ-system aging can be broadly characterized as the onset and progression of the twelve hallmarks of aging leading to an increased susceptibility to chronic age-related diseases, cancers and death with associated socioeconomic consequences [47] [48]. In the past decade, small molecule-based therapies, leveraging on transcription factors, and reprogramming intervention strategies for epigenetic rejuvenation are being considered to reduce or reverse these infirmities through modifications of epigenetic marks and gene expression patterns. Currently, reprogramming research has focused on two different but related means, namely complete reprogramming and partial reprogramming.

4.1. Complete Reprogramming Strategies

The advent of induced pluripotent stem cells (iPSCs) following the discovery of Shinya Yamanaka (2012 Nobel prize in Medicine) brought about a regenerative medicine approach to virtually every human condition possibility including aging skin, fat loss, and alopecia [49]. This *in vitro* research allowed reprogramming of human somatic differentiated cells (e.g., skin cells) to induce pluripotent stem cells (iPSCs). The landmark paper used four transcription factors, namely OCT4, SOX2, KLF4, and MYC (0SKM cocktail) to remove cell identity and reset cell-type-specific epigenetic signatures [50]. Other investigators [51] [52] have employed the same canonical OSKM factors to induce complete return to pluripo-

tential cells in various mouse and human somatic cell types. Oct4 is considered the master transcriptional regulator of epigenetic reprogramming, in that its overexpression alone can induce pluripotential regression [53]-[55]. SOX2 has multiple roles as a transcription factor involved in embryonic development, cancer biology, and a primer that first attaches to the chromatin before subsequent OCT4 binding [56] [57]. The close association of shared binding sites for OCT4/SOX2 enables significant accessibility for epigenetic reprogramming and induced pluripotency [58]. KLF4 acts synergistically with OCT4/SOX2 to increase accessibility during complete iPSC reprogramming, and is thought to initiate the first onset of transcriptional activation [59]. In contrast to OSK factors, MYC is considered a potent amplifier of reprogramming [60] rather than an instigator of the induction process [61]. Other transcription factors NANOG and LIN28 are also being studied as alternatives to canonical OKSM factors because they share 90% binding sites of OCT4 and SOX2 [59]. When these 2 factors are combined with OCT4/SOX2 [52], their synergistic effects can increase the reprogramming efficiency by 76-fold for reprogramming human somatic cells into iPSCs [62]. Although these breakthrough revelations with full cell reprogramming show great promise for reversing the aging process and chronic diseases, the observed phenomena of frequent tissue dysplasia and tumorigenesis diminishes its acceptance as an appropriate or viable alternative for anti-aging strategies. For example, continuous expression of OSKM factors *in vivo* is limited by substantial safety concerns such as severe weight loss, the formation of totipotent stem cells and teratomas in several organ systems [63].

4.2. Partial Reprogramming Strategies

Partial reprogramming [64]-[67] has the potential of reversing aging by resetting the landscape safely without reaching a pluripotency state to achieve rejuvenation while preserving cell identity and minimizing tumorigenesis. In addition, partial reprogramming influences major hallmarks such as autophagy and mitochondrial membrane potentials [68]. This approach uses combinations of the Yamanaka OSKM transcriptional activators to initiate the first steps toward pluripotency by evoking somatic silencing and chromatin nucleosome closures [69]-[71]. The mechanisms for silencing gene activation that become inaccessible after OSKM induction are not fully understood but may involve displacement or down-regulation of the transcription factors [72] [73]. As somatic programs are silenced, transcriptional remodeling of canonical OCT4/MYC/KLF4 and SOX2 factors occurs that drive the reprogramming of somatic cells to iPS cells [74] [75]. OSKN also resets the epigenetic landscape by inducing changes to histone tail post-transitional modifications by DNA methylation [76] [77], The precise mechanism(s) of how histone methylation affects transcriptional functions of activation and repressions is unclear and needs to be defined. DNA methylation during iPS cell reprogramming facilitates the interplay between chromatin remodeling as well as silencing differentiation-associated genes [78] [79]. The road map for reprogram-

ming from beginning to end remains a challenge to navigate because events are transient, contradictory, and dynamic in their interactions.

4.3. Partial Reprogramming for Epigenetic Rejuvenation

The concept of epigenetic rejuvenation, defined as inducing epigenetic changes by partial reprogramming to a younger rejuvenated state without loss of identity, was first proposed in 2021 [80] [81]. Since then, substantial progress has been made to develop safer and more effective partial reprogramming protocols [82], including but not limited, to optimizing cyclic [68] [83], or continuous [84] [85] expression, single [86] or long-term expression [87], levels of expression [71] [88], and partial de-differentiation reprogamming [70] [88] to induce epigenetic rejuvenation without losing cell identity via partial de-differentiation in mice models. Through careful pulsing OSKM expression in whole older mice, Ocampo and colleagues' partial reprogramming protocol improved cellular physiological aging markers without formation of teratomas [68]. However, the rejuvenation effects were transient after termination of OSKM expression. Additionally, Chondronasion's study [86] of a single pulse of continuous OSKM induction for seven days in naturally aged mice emphasized how OSKM over expression can result in drastically different effects on different cell types with the same organ. Experiments in mice clearly provided evidence that partial epigenetic reprogramming can reverse aspects of aging.

Although experiments in rodents provided foundational evidence that epigenetic reprogramming can reverse aspects of aging, these effects have yet to be fully translated in human cells and tissue. Initial experiments with human cells demonstrated that some biomarkers of aging responded to epigenetic reprogramming through re-differentiation after iPS cell formation. For example, early investigations in human cells were somewhat encouraging with observations of shortening of telomere lengths with protocols relying on rejuvenation through re-differentiation after iPS formation [89]-[92]. Manukyan and colleagues made the first attempt to optimize the reprogramming process by adding microRNA let-7 to the OSKM cocktail to restore senescent human fibroblasts to younger cells without loss of cell identity [81]. More recently, Sarkar *et al.* [92] obtained the first evidence of partial reprogramming-induced rejuvenation of aging human cells in vitro by using a messenger RNA-based strategy for transient expression of six factors, OSKM, LIN28, and NANOG (OSKMLN). The extent of OSKMLN reprogramming was multifaceted and far-reaching, as epigenetic hallmarks, functional parameters, and epigenetic clocks were significant compared to age-matched counterparts. Although significant progress has been accomplished concerning safe and effective reprogramming cocktails, timing, and duration of induction have yet to be optimized before their implementation in patients because of potential and unknown side effects and risks. That said, partial reprogramming strategies to reverse aging without a pluripotential state or loss of cellular identity have remained challenging for human trials because of contradictory and transient re-

sults with *in vitro* and translational studies. During partial reprogramming events, somatic skin cells undergo multiple intermediate stages during epigenetic, transcription factor-induced remodeling and cell identity conservation. Somatic silencing, the earliest reprogramming event, is tightly regulated by OSK transcriptional activator factors that suggest OSK induce silencing of gene-associated chromatin loci through direct or indirect mechanisms. During the intermediate stages, an incomplete almost pluripotent cell type emerges, as opposed to a true pluripotent cell. All transcriptional remodeling investigations utilizing OSKM occupancy data are limited to events that occur in the beginning or end points with everything in between still up for interpretation. As early events are largely transient, identifying markers during the critical intermediate phase remain largely unanswered. Despite these concerns, commercial companies have explored the use of *in vivo* partial reprogramming (IVPR) treatments in the last few years. Their therapeutic clinical applications are still limited until partial reprogramming methods become safe and effective [93].

4.4. Alternative Partial Reprogramming Strategies

Because of the potential uncertainties in reprogramming strategies using transcription factors, researchers [94] [95] have focused also on small molecular compounds, less than 500 Dalton in size, such as methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors to target any portion of enzymes, receptors and signaling pathways. DNA methyltransferase catalyzed the addition of methyl groups to cytosine residues located in the CpG dinucleotides to regulated gene expression [96]. When abnormal DNA methylation patterns linked to aging or diseases occur, DNMT inhibitors can delay or reverse them emerged as a potential anti-aging strategy. Several DNMT inhibitors such as 5-azacitidine, a cytidine analog, has been found to inhibit DNA methylation [97], producing hypomethylation for reversal of age-related patterns in immune cells, stem cells and neurons [98]. Of interest, the application of 5-AZA reversed phenotypic aging in human adipose-derived stem cells, suggesting its possibility to slow down and even reverse age-related findings in stem cells [99]. However, the safety profile of AZA used as a chemotherapeutic drug in patients with myelodysplastic syndromes exhibits significant serious side effects and risks such as anemia, thrombocytopenia and neutropenia and renal damage [100].

Cellular aging is also associated with changes in histone acetylation of core histones that are regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [101]. Acetylation neutralizes the interaction between histones and DNA, allowing accessibility for increased transcriptional activity. In contrast, HDACs remove acetyl groups from histone lysine that condenses spacing and represses transcription. The action of HDAC inhibitors targets the active sites of various HDAC enzymes inducing gene activation that has the potential to improve telomere lengthening, DNA repair, proteostasis, mitochondrial dysfunction, and cellular senescence [102]. In summary, HDAC

inhibitors are demonstrating promising results in preclinical studies to rejuvenate aging cells by partial reprogramming of the epigenetic pathways [103] [104].

5. Conclusions

Throughout the history of humanity, the search to extend healthspan and lifespan has been a persistent goal. Modern theories in aging research have focused on degenerative changes in DNA and mutations, which overtime lead to genomic malfunctioning to infirmity, chronic diseases, and cancer. More recently, the emergence of epigenetics has increased our understanding that epigenetic remodeling expands the intimate relationship between chromatin and epigenetic influences on slowing or reversing the aging processes. The advent of partial reprogramming epigenetic protocols has further altered our concepts of potentially reversing aged or diseased cells by identifying key check points along the rejuvenation pathway without cancer risks and loss of cell identity before they reach the point of no return at their final embryonic cell state. In this regard, research is studying whether partial de-differentiation or re-differentiation are crucial steps for effective safe rejuvenation. Various rejuvenation protocols provide insights and strategies for ameliorating age-related chronic diseases, including, but not limited, to removal of senescence cells and suppression of their associated secretory phenotypes, metabolic changes, stem cell therapies, and immune augmentation.

Despite the rapid advances in cellular and tissue rejuvenation as a potential for treating human diseases, cellular partial reprograming strategies are still in their infancy with low efficiency rates, yet to be resolved issues of over-expression of transcription factors, and control of potential safety issues [105]. During incomplete reprogramming, for example, cells might not begin the induction process, while others are terminated at varying intermediate stages, resulting in a mixed heterogeneous population of reverted cells in various stages of rejuvenation. Additionally, the extent of rejuvenation without complete dedifferentiation has been observed to be insufficient, as well as not all cells uniformly regain or retain their youthful characteristics. These varying degrees of expression of reprogramming factor, and therefore the total amount of reprogramming, among different cells, tissue types, and organs, have resulted in varying outcomes in lifespan extensions, uniform reversal epigenetic hallmarks, and impaired tissue regeneration from *in vivo* translational studies. Other factors that contribute to low efficiency include delivering OSKM transcription factors consistently and efficiently into cells, identifying potential biomarkers of subpopulations with enhanced reprogramming potential, overcoming barriers of epigenetic modifications, intrinsic resistance of senescent cells to reprogramming, and refining optimal factor combinations of timing, dosage, and duration. Currently, the pre-clinical use of RNA-based protocols [106], modification of OKSM genes, and small molecules chromatin activators will require more comprehensive and standardized investigations to establish safety and efficacy in humans.

Funding

The author received no funding for this manuscript.

Conflicts of Interest

The author declares no conflict of interest.

References

[1] López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M. and Kroemer, G. (2023) Hallmarks of Aging: An Expanding Universe. *Cell*, **186**, 243-278. https://doi.org/10.1016/j.cell.2022.11.001

[2] Booth, L.N. and Brunet, A. (2016) The Aging Epigenome. *Molecular Cell*, **62**, 728-744.

[3] Oberdoeffer, P. and Sinclair, D.A. (2007) The Role of Nuclear Architecture in Genomic Instability and Ageing. *Nature Reviews Molecular Cell Biology*, **8**, 692-702.

[4] Zhang, W., Qu, J., Liu, G. and Belmonte, J.C.I. (2020) The Ageing Epigenome and Its Rejuvenation. *Nature Reviews Molecular Cell Biology*, **21**, 137-150. https://doi.org/10.1038/s41580-019-0204-5

[5] Campisi, J. and Vijg, J. (2009) Does Damage to DNA and Other Macromolecules Play a Role in Aging? If So, How? *The Journals of Gerontology Series A*: *Biological Sciences and Medical Sciences*, **64**, 175-178. https://doi.org/10.1093/gerona/gln065

[6] Alle, Q., Borgne, E.L., Milhavet, O., *et al.* (2021) Reprogramming: Emerging Strategies to Rejuvenate Aging Cells and Tissues. *International Journal of Molecular Sciences*, **22**, Article 3990.

[7] Yu, M., Hazelton, W.D., Luebeck, G.E. and Grady, W.M. (2020) Epigenetic Aging: More than Just a Clock When It Comes to Cancer. *Cancer Research*, **80**, 367-374. https://doi.org/10.1158/0008-5472.can-19-0924

[8] Wang, K., Liu, H., Hu, Q., *et al.* (2022) Epigenetic Regulations of Aging: Implications for Interventions of Aging and Disease. *Signal Transduction and Targeted Therapy*, **7**, Article 374.

[9] Dhar, P., Moodithaya, S.S. and Patil, P. (2022) Epigenetic Alterations—The Silent Indicator for Early Aging and Age-Associated Health-Risks. *Aging Medicine*, **5**, 287-293. https://doi.org/10.1002/agm2.12236

[10] Li, A., Koch, Z. and Ideker, T. (2022) Epigenetic Aging: Biological Age Prediction and Informing a Mechanistic Theory of Aging. *Journal of Internal Medicine*, **292**, 733-744. https://doi.org/10.1111/joim.13533

[11] Cheutin, T., McNairn, A.J., Jenuwein, T., Gilbert, D.M., Singh, P.B. and Misteli, T. (2003) Maintenance of Stable Heterochromatin Domains by Dynamic HP1 Binding. *Science*, **299**, 721-725. https://doi.org/10.1126/science.1078572

[12] Obe, G., Pfeiffer, P., Savage, J.R.K., Johannes, C., Goedecke, W., Jeppesen, P., *et al.* (2002) Chromosomal Aberrations: Formation, Identification and Distribution. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, **504**, 17-36. https://doi.org/10.1016/s0027-5107(02)00076-3

[13] Grewal, S.I.S. and Jia, S. (2007) Heterochromatin Revisited. *Nature Reviews Genetics*, **8**, 35-46. https://doi.org/10.1038/nrg2008

[14] Jenuwein, T. and Allis, C.D. (2001) Translating the Histone Code. *Science*, **293**, 1074-1080. https://doi.org/10.1126/science.1063127

[15] Birney, E., Stamatoyannopoulos, J.A., Dutta, A., *et al.* (2007) Identification and Analysis of Functional Elements in 1% of the Human Genome by the ENCODE Pilot Project. *Nature*, **447**, 799-816. https://doi.org/10.1038/nature05874

[16] Kharchenko, P.V., Alekseyenko, A.A., Schwartz, Y.B., Minoda, A., Riddle, N.C., Ernst, J., *et al.* (2010) Comprehensive Analysis of the Chromatin Landscape in Drosophila Melanogaster. *Nature*, **471**, 480-485. https://doi.org/10.1038/nature09725

[17] Jones, M.J., Goodman, S.J. and Kobor, M.S. (2015) DNA Methylation and Healthy Human Aging. *Aging Cell*, **14**, 924-932. https://doi.org/10.1111/acel.12349

[18] Berdyshev, G.D., Korotaev, G.K., Boiarskikh, G.V., *et al.* (1967) Nucleotide Composition of DNA and RNA from Somatic Tissues of Humpback and Its Changes during Spawning. *Biokhimiia*, **32**, 988-993.

[19] Rakyan, V.K., Down, T.A., Maslau, S., Andrew, T., Yang, T., Beyan, H., *et al.* (2010) Human Aging-Associated DNA Hypermethylation Occurs Preferentially at Bivalent Chromatin Domains. *Genome Research*, **20**, 434-439. https://doi.org/10.1101/gr.103101.109

[20] Teschendorff, A.E., Menon, U., Gentry-Maharaj, A., Ramus, S.J., Weisenberger, D.J., Shen, H., *et al.* (2010) Age-Dependent DNA Methylation of Genes That Are Suppressed in Stem Cells Is a Hallmark of Cancer. *Genome Research*, **20**, 440-446. https://doi.org/10.1101/gr.103606.109

[21] Koch, C.M. and Wagner, W. (2011) Epigenetic-Aging-Signature to Determine Age in Different Tissues. *Aging*, **3**, 1018-1027. https://doi.org/10.18632/aging.100395

[22] Jylhävä, J., Pedersen, N.L. and Hägg, S. (2017) Biological Age Predictors. *eBioMedicine*, **21**, 29-36. https://doi.org/10.1016/j.ebiom.2017.03.046

[23] Levine, M.E., Lu, A.T., Quach, A., Chen, B.H., Assimes, T.L., Bandinelli, S., *et al.* (2018) An Epigenetic Biomarker of Aging for Lifespan and Healthspan. *Aging*, **10**, 573-591. https://doi.org/10.18632/aging.101414

[24] Jin, K. (2010) Modern Biological Theories of Aging. *Aging and Disease*, **1**, L72-L74.

[25] López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M. and Kroemer, G. (2013) The Hallmarks of Aging. *Cell*, **153**, 1194-1217. https://doi.org/10.1016/j.cell.2013.05.039

[26] Bocklandt, S., Lin, W., Sehl, M.E., Sánchez, F.J., Sinsheimer, J.S., Horvath, S., *et al.* (2011) Epigenetic Predictor of Age. *PLOS ONE*, **6**, e14821. https://doi.org/10.1371/journal.pone.0014821

[27] Hannum, G., Guinney, J., Zhao, L., Zhang, L., Hughes, G., Sadda, S., *et al.* (2013) Genome-Wide Methylation Profiles Reveal Quantitative Views of Human Aging Rates. *Molecular Cell*, **49**, 359-367. https://doi.org/10.1016/j.molcel.2012.10.016

[28] Horvath, S. (2013) DNA Methylation Age of Human Tissues and Cell Types. *Genome Biology*, **14**, Article No. 3156. https://doi.org/10.1186/gb-2013-14-10-r115

[29] Horvath, S. and Raj, K. (2018) DNA Methylation-Based Biomarkers and the Epigenetic Clock Theory of Ageing. *Nature Reviews Genetics*, **19**, 371-384. https://doi.org/10.1038/s41576-018-0004-3

[30] Lu, A.T., Quach, A., Wilson, J.G., Reiner, A.P., Aviv, A., Raj, K., *et al.* (2019) DNA Methylation Grimage Strongly Predicts Lifespan and Health Span. *Aging*, **11**, 303-327. https://doi.org/10.18632/aging.101684

[31] Belsky, D.W., Caspi, A., Arseneault, L., Baccarelli, A., Corcoran, D.L., Gao, X., *et al.* (2020) Quantification of the Pace of Biological Aging in Humans through a Blood Test, the Dunedinpoam DNA Methylation Algorithm. *eLife*, **9**, e54870. https://doi.org/10.7554/elife.54870

[32] Gensous, N., Bacalini, M.G., Pirazzini, C., Marasco, E., Giuliani, C., Ravaioli, F., *et al.* (2017) The Epigenetic Landscape of Age-Related Diseases: The Geroscience Perspective. *Biogerontology*, **18**, 549-559. https://doi.org/10.1007/s10522-017-9695-7

[33] Nannini, D.R., Joyce, B.T., Zheng, Y., Gao, T., Liu, L., Yoon, G., *et al.* (2019) Epigenetic Age Acceleration and Metabolic Syndrome in the Coronary Artery Risk Development in Young Adults Study. *Clinical Epigenetics*, **11**, Article No. 160. https://doi.org/10.1186/s13148-019-0767-1

[34] Sillanpää, E., Heikkinen, A., Kankaanpää, A., Paavilainen, A., Kujala, U.M., Tammelin, T.H., *et al.* (2021) Blood and Skeletal Muscle Ageing Determined by Epigenetic Clocks and Their Associations with Physical Activity and Functioning. *Clinical Epigenetics*, **13**, Article No. 110. https://doi.org/10.1186/s13148-021-01094-6

[35] Ecker, S. and Beck, S. (2019) The Epigenetic Clock: A Molecular Crystal Ball for Human Aging? *Aging*, **11**, 833-835. https://doi.org/10.18632/aging.101712

[36] Barzilai, N., Huffman, D.M., Muzumdar, R.H. and Bartke, A. (2012) The Critical Role of Metabolic Pathways in Aging. *Diabetes*, **61**, 1315-1322. https://doi.org/10.2337/db11-1300

[37] Trifunovic, A., Wredenberg, A., Falkenberg, M., Spelbrink, J.N., Rovio, A.T., Bruder, C.E., *et al.* (2004) Premature Ageing in Mice Expressing Defective Mitochondrial DNA Polymerase. *Nature*, **429**, 417-423. https://doi.org/10.1038/nature02517

[38] Kabacik, S., Lowe, D., Fransen, L., Leonard, M., Ang, S., Whiteman, C., *et al.* (2022) The Relationship between Epigenetic Age and the Hallmarks of Aging in Human Cells. *Nature Aging*, **2**, 484-493. https://doi.org/10.1038/s43587-022-00220-0

[39] Lowe, D., Horvath, S. and Raj, K. (2016) Epigenetic Clock Analyses of Cellular Senescence and Ageing. *Oncotarget*, **7**, 8524-8531. https://doi.org/10.18632/oncotarget.7383

[40] Bodnar, A.G., Ouellette, M., Frolkis, M., Holt, S.E., Chiu, C., Morin, G.B., *et al.* (1998) Extension of Life-Span by Introduction of Telomerase into Normal Human Cells. *Science*, **279**, 349-352. https://doi.org/10.1126/science.279.5349.349

[41] Lowe, D.J., Herzog, M., Mosler, T., Cohen, H., Felton, S., Beli, P., *et al.* (2020) Chronic Irradiation of Human Cells Reduces Histone Levels and Deregulates Gene Expression. *Scientific Reports*, **10**, Article No. 2200. https://doi.org/10.1038/s41598-020-59163-4

[42] Bienkowska, A., Raddatz, G., Söhle, J., Kristof, B., Völzke, H., Gallinat, S., *et al.* (2024) Development of an Epigenetic Clock to Predict Visual Age Progression of Human Skin. *Frontiers in Aging*, **4**, Article 1258183. https://doi.org/10.3389/fragi.2023.1258183

[43] Boroni, M., Zonari, A., Reis de Oliveira, C., Alkatib, K., Ochoa Cruz, E.A., Brace, L.E., *et al.* (2020) Highly Accurate Skin-Specific Methylome Analysis Algorithm as a Platform to Screen and Validate Therapeutics for Healthy Aging. *Clinical Epigenetics*, **12**, Article No. 105. https://doi.org/10.1186/s13148-020-00899-1

[44] Jeltsch, A. and Jurkowska, R.Z. (2014) New Concepts in DNA Methylation. *Trends in Biochemical Sciences*, **39**, 310-318. https://doi.org/10.1016/j.tibs.2014.05.002

[45] Ushijima, T., Watanabe, N., Okochi, E., Kaneda, A., Sugimura, T. and Miyamoto, K. (2003) Fidelity of the Methylation Pattern and Its Variation in the Genome. *Genome Research*, **13**, 868-874. https://doi.org/10.1101/gr.969603

[46] Luebeck, G.E., Hazelton, W.D., Curtius, K., Maden, S.K., Yu, M., Carter, K.T., *et al.* (2019) Implications of Epigenetic Drift in Colorectal Neoplasia. *Cancer Research*, **79**,

495-504. https://doi.org/10.1158/0008-5472.can-18-1682

[47] Fakouri, N.B., Hou, Y., Demarest, T.G., Christiansen, L.S., Okur, M.N., Mohanty, J.G., *et al.* (2018) Toward Understanding Genomic Instability, Mitochondrial Dysfunction and Aging. *The FEBS Journal*, **286**, 1058-1073. https://doi.org/10.1111/febs.14663

[48] Guo, J., Huang, X., Dou, L., Yan, M., Shen, T., Tang, W., *et al.* (2022) Aging and Aging-Related Diseases: From Molecular Mechanisms to Interventions and Treatments. *Signal Transduction and Targeted Therapy*, **7**, Article No. 391. https://doi.org/10.1038/s41392-022-01251-0

[49] Takahashi, K. and Yamanaka, S. (2006) Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, **126**, 663-676. https://doi.org/10.1016/j.cell.2006.07.024

[50] Al Abbar, A., Ngai, S.C., Nograles, N., Alhaji, S.Y. and Abdullah, S. (2020) Induced Pluripotent Stem Cells: Reprogramming Platforms and Applications in Cell Replacement Therapy. *BioResearch Open Access*, **9**, 121-136. https://doi.org/10.1089/biores.2019.0046

[51] Park, I., Zhao, R., West, J.A., Yabuuchi, A., Huo, H., Ince, T.A., *et al.* (2007) Reprogramming of Human Somatic Cells to Pluripotency with Defined Factors. *Nature*, **451**, 141-146. https://doi.org/10.1038/nature06534

[52] Yu, J., Vodyanik, M.A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J.L., Tian, S., *et al.* (2007) Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells. *Science*, **318**, 1917-1920. https://doi.org/10.1126/science.1151526

[53] Kim, K., Han, D.W., Kim, J. and Schöler, H.R. (2021) Biological Importance of OCT Transcription Factors in Reprogramming and Development. *Experimental & Molecular Medicine*, **53**, 1018-1028. https://doi.org/10.1038/s12276-021-00637-4

[54] Radzisheuskaya, A. and Silva, J.C.R. (2014) Do All Roads Lead to Oct4? The Emerging Concepts of Induced Pluripotency. *Trends in Cell Biology*, **24**, 275-284. https://doi.org/10.1016/j.tcb.2013.11.010

[55] Papapetrou, E.P., Tomishima, M.J., Chambers, S.M., Mica, Y., Reed, E., Menon, J., *et al.* (2009) Stoichiometric and Temporal Requirements of Oct4, Sox2, Klf4, and c-Myc Expression for Efficient Human iPSC Induction and Differentiation. *Proceedings of the National Academy of Sciences*, **106**, 12759-12764. https://doi.org/10.1073/pnas.0904825106

[56] Novak, D., Hüser, L., Elton, J.J., Umansky, V., Altevogt, P. and Utikal, J. (2020) SOX2 in Development and Cancer Biology. *Seminars in Cancer Biology*, **67**, 74-82. https://doi.org/10.1016/j.semcancer.2019.08.007

[57] Chen, J., Zhang, Z., Li, L., Chen, B., Revyakin, A., Hajj, B., *et al.* (2014) Single-Molecule Dynamics of Enhanceosome Assembly in Embryonic Stem Cells. *Cell*, **156**, 1274-1285. https://doi.org/10.1016/j.cell.2014.01.062

[58] Malik, V., Glaser, L.V., Zimmer, D., Velychko, S., Weng, M., Holzner, M., *et al.* (2019) Pluripotency Reprogramming by Competent and Incompetent POU Factors Uncovers Temporal Dependency for Oct4 and Sox2. *Nature Communications*, **10**, Article No. 3477. https://doi.org/10.1038/s41467-019-11054-7

[59] Jerabek, S., Ng, C.K., Wu, G., Arauzo-Bravo, M.J., Kim, K., Esch, D., *et al.* (2016) Changing POU Dimerization Preferences Converts Oct6 into a Pluripotency Inducer. *EMBO Reports*, **18**, 319-333. https://doi.org/10.15252/embr.201642958

[60] Smith, Z.D., Sindhu, C. and Meissner, A. (2016) Molecular Features of Cellular Reprogramming and Development. *Nature Reviews Molecular Cell Biology*, **17**, 139-

154. https://doi.org/10.1038/nrm.2016.6

[61] Nakagawa, M., Koyanagi, M., Tanabe, K., Takahashi, K., Ichisaka, T., Aoi, T., *et al.* (2007) Generation of Induced Pluripotent Stem Cells without Myc from Mouse and Human Fibroblasts. *Nature Biotechnology*, **26**, 101-106. https://doi.org/10.1038/nbt1374

[62] Wang, L., Su, Y., Huang, C., Yin, Y., Chu, A., Knupp, A., *et al.* (2019) NANOG and LIN28 Dramatically Improve Human Cell Reprogramming by Modulating LIN41 and Canonical WNT Activities. *Biology Open*, **8**, bio047225. https://doi.org/10.1242/bio.047225

[63] Abad, M., Mosteiro, L., Pantoja, C., Cañamero, M., Rayon, T., Ors, I., *et al.* (2013) Reprogramming *in Vivo* Produces Teratomas and Ips Cells with Totipotency Features. *Nature*, **502**, 340-345. https://doi.org/10.1038/nature12586

[64] Galow, A. and Peleg, S. (2022) How to Slow down the Ticking Clock: Age-Associated Epigenetic Alterations and Related Interventions to Extend Life Span. *Cells*, **11**, Article 468. https://doi.org/10.3390/cells11030468

[65] Ji, S., Xiong, M., Chen, H., Liu, Y., Zhou, L., Hong, Y., *et al.* (2023) Cellular Rejuvenation: Molecular Mechanisms and Potential Therapeutic Interventions for Diseases. *Signal Transduction and Targeted Therapy*, **8**, Article No. 116. https://doi.org/10.1038/s41392-023-01343-5

[66] Puri, D. and Wagner, W. (2023) Epigenetic Rejuvenation by Partial Reprogramming. *BioEssays*, **45**, Article 2200208. https://doi.org/10.1002/bies.202200208

[67] Singh, P.B. and Zhakupova, A. (2022) Age Programming: Cell Rejuvenation by Partial Reprogramming. *Development*, **149**, dev200755.

[68] Ocampo, A., Reddy, P., Martinez-Redondo, P., Platero-Luengo, A., Hatanaka, F., Hishida, T., *et al.* (2016) *In Vivo* Amelioration of Age-Associated Hallmarks by Partial Reprogramming. *Cell*, **167**, 1719-1733. https://doi.org/10.1016/j.cell.2016.11.052

[69] Gill, D., Parry, A., Santos, F., Okkenhaug, H., Todd, C.D., Hernando-Herraez, I., *et al.* (2022) Multi-Omic Rejuvenation of Human Cells by Maturation Phase Transient Reprogramming. *eLife*, **11**, e71624. https://doi.org/10.7554/elife.71624

[70] Guo, L., Karoubi, G., Duchesneau, P., Shutova, M.V., Sung, H., Tonge, P., *et al.* (2017) Generation of Induced Progenitor-Like Cells from Mature Epithelial Cells Using Interrupted Reprogramming. *Stem Cell Reports*, **9**, 1780-1795. https://doi.org/10.1016/j.stemcr.2017.10.022

[71] Hishida, T., Yamamoto, M., Hishida-Nozaki, Y., Shao, C., Huang, L., Wang, C., *et al.* (2022) *In Vivo* Partial Cellular Reprogramming Enhances Liver Plasticity and Regeneration. *Cell Reports*, **39**, Article 110730. https://doi.org/10.1016/j.celrep.2022.110730

[72] Chronis, C., Fiziev, P., Papp, B., Butz, S., Bonora, G., Sabri, S., *et al.* (2017) Cooperative Binding of Transcription Factors Orchestrates Reprogramming. *Cell*, **168**, 442-459. https://doi.org/10.1016/j.cell.2016.12.016

[73] Li, D., Liu, J., Yang, X., Zhou, C., Guo, J., Wu, C., *et al.* (2017) Chromatin Accessibility Dynamics during IPSC Reprogramming. *Cell Stem Cell*, **21**, 819-833. https://doi.org/10.1016/j.stem.2017.10.012

[74] Knaupp, A.S., Buckberry, S., Pflueger, J., Lim, S.M., Ford, E., Larcombe, M.R., *et al.* (2017) Transient and Permanent Reconfiguration of Chromatin and Transcription Factor Occupancy Drive Reprogramming. *Cell Stem Cell*, **21**, 834-845. https://doi.org/10.1016/j.stem.2017.11.007

[75] Narayan, S., Bryant, G., Shah, S., Berrozpe, G. and Ptashne, M. (2017) OCT4 and SOX2 Work as Transcriptional Activators in Reprogramming Human Fibroblasts. *Cell Reports*, **20**, 1585-1596. https://doi.org/10.1016/j.celrep.2017.07.071

[76] Polo, J.M., Anderssen, E., Walsh, R.M., Schwarz, B.A., Nefzger, C.M., Lim, S.M., *et al.* (2012) A Molecular Roadmap of Reprogramming Somatic Cells into Ips Cells. *Cell*, **151**, 1617-1632. https://doi.org/10.1016/j.cell.2012.11.039

[77] Schwarz, B.A., Cetinbas, M., Clement, K., Walsh, R.M., Cheloufi, S., Gu, H., *et al.* (2018) Prospective Isolation of Poised IPSC Intermediates Reveals Principles of Cellular Reprogramming. *Cell Stem Cell*, **23**, 289-305. https://doi.org/10.1016/j.stem.2018.06.013

[78] Lee, D., Shin, J., Tonge, P.D., Puri, M.C., Lee, S., Park, H., *et al.* (2014) An Epigenomic Roadmap to Induced Pluripotency Reveals DNA Methylation as a Reprogramming Modulator. *Nature Communications*, **5**, Article No. 5619. https://doi.org/10.1038/ncomms6619

[79] Papp, B. and Plath, K. (2013) Epigenetics of Reprogramming to Induced Pluripotency. *Cell*, **152**, 1324-1343. https://doi.org/10.1016/j.cell.2013.02.043

[80] Singh, P.B. and Zacouto, F. (2010) Nuclear Reprogramming and Epigenetic Rejuvenation. *Journal of Biosciences*, **35**, 315-319. https://doi.org/10.1007/s12038-010-0034-2

[81] Manukyan, M. and Singh, P.B. (2012) Epigenetic Rejuvenation. *Genes to Cells*, **17**, 337-343. https://doi.org/10.1111/j.1365-2443.2012.01595.x

[82] Cipriano, A., Moqri, M., Maybury-Lewis, S.Y., Rogers-Hammond, R., de Jong, T.A., Parker, A., *et al.* (2023) Mechanisms, Pathways and Strategies for Rejuvenation through Epigenetic Reprogramming. *Nature Aging*, **4**, 14-26. https://doi.org/10.1038/s43587-023-00539-2

[83] Rodríguez-Matellán, A., Alcazar, N., Hernández, F., Serrano, M. and Ávila, J. (2020) *In Vivo* Reprogramming Ameliorates Aging Features in Dentate Gyrus Cells and Improves Memory in Mice. *Stem Cell Reports*, **15**, 1056-1066. https://doi.org/10.1016/j.stemcr.2020.09.010

[84] Alle, Q., Le Borgne, E., Bensadoun, P., Lemey, C., Béchir, N., Gabanou, M., *et al.* (2022) A Single Short Reprogramming Early in Life Initiates and Propagates an Epigenetically Related Mechanism Improving Fitness and Promoting an Increased Healthy Lifespan. *Aging Cell*, **21**, e13714. https://doi.org/10.1111/acel.13714

[85] Lu, Y., Brommer, B., Tian, X., Krishnan, A., Meer, M., Wang, C., *et al.* (2020) Reprogramming to Recover Youthful Epigenetic Information and Restore Vision. *Nature*, **588**, 124-129. https://doi.org/10.1038/s41586-020-2975-4

[86] Chondronasiou, D., Gill, D., Mosteiro, L., Urdinguio, R.G., Berenguer-Llergo, A., Aguilera, M., *et al.* (2022) Multi-Omic Rejuvenation of Naturally Aged Tissues by a Single Cycle of Transient Reprogramming. *Aging Cell*, **21**, e13578. https://doi.org/10.1111/acel.13578

[87] Browder, K.C., Reddy, P., Yamamoto, M., Haghani, A., Guillen, I.G., Sahu, S., *et al.* (2022) *In Vivo* Partial Reprogramming Alters Age-Associated Molecular Changes during Physiological Aging in Mice. *Nature Aging*, **2**, 243-253. https://doi.org/10.1038/s43587-022-00183-2

[88] Roux, A.E., Zhang, C., Paw, J., Zavala-Solorio, J., Malahias, E., Vijay, T., *et al.* (2022) Diverse Partial Reprogramming Strategies Restore Youthful Gene Expression and Transiently Suppress Cell Identity. *Cell Systems*, **13**, 574-587. https://doi.org/10.1016/j.cels.2022.05.002

[89] Marión, R.M., López de Silanes, I., Mosteiro, L., Gamache, B., Abad, M., Guerra, C., *et al.* (2017) Common Telomere Changes during *in Vivo* Reprogramming and Early Stages of Tumorigenesis. *Stem Cell Reports*, **8**, 460-475. https://doi.org/10.1016/j.stemcr.2017.01.001

[90] Lapasset, L., Milhavet, O., Prieur, A., Besnard, E., Babled, A., Aït-Hamou, N., *et al.* (2011) Rejuvenating Senescent and Centenarian Human Cells by Reprogramming through the Pluripotent State. *Genes & Development*, **25**, 2248-2253. https://doi.org/10.1101/gad.173922.111

[91] Suhr, S.T., Chang, E.A., Rodriguez, R.M., Wang, K., Ross, P.J., Beyhan, Z., *et al.* (2009) Telomere Dynamics in Human Cells Reprogrammed to Pluripotency. *PLOS ONE*, **4**, e8124. https://doi.org/10.1371/journal.pone.0008124

[92] Sarkar, T.J., Quarta, M., Mukherjee, S., Colville, A., Paine, P., Doan, L., *et al.* (2020) Transient Non-Integrative Expression of Nuclear Reprogramming Factors Promotes Multifaceted Amelioration of Aging in Human Cells. *Nature Communications*, **11**, Article No. 1545. https://doi.org/10.1038/s41467-020-15174-3

[93] Paine, P.T., Nguyen, A. and Ocampo, A. (2023) Partial Cellular Reprogramming: A Deep Dive into an Emerging Rejuvenation Technology. *Aging Cell*, **23**, e14039. https://doi.org/10.1111/acel.14039

[94] Kim, Y., Jeong, J. and Choi, D. (2020) Small-Molecule-Mediated Reprogramming: A Silver Lining for Regenerative Medicine. *Experimental & Molecular Medicine*, **52**, 213-226. https://doi.org/10.1038/s12276-020-0383-3

[95] Megino-Luque, C., Moiola, C.P., Molins-Escuder, C., López-Gil, C., Gil-Moreno, A., Matias-Guiu, X., *et al.* (2020) Small-Molecule Inhibitors (SMIs) as an Effective Therapeutic Strategy for Endometrial Cancer. *Cancers*, **12**, Article 2751. https://doi.org/10.3390/cancers12102751

[96] Xiao, F., Wang, H. and Kong, Q. (2019) Dynamic DNA Methylation during Aging: A "Prophet" of Age-Related Outcomes. *Frontiers in Genetics*, **10**, Article 107. https://doi.org/10.3389/fgene.2019.00107

[97] Xu, H., Li, S. and Liu, Y. (2021) Roles and Mechanisms of DNA Methylation in Vascular Aging and Related Diseases. *Frontiers in Cell and Developmental Biology*, **9**, Article 699374. https://doi.org/10.3389/fcell.2021.699374

[98] Giri, A.K. and Aittokallio, T. (2019) DNMT Inhibitors Increase Methylation in the Cancer Genome. *Frontiers in Pharmacology*, **10**, Article 385. https://doi.org/10.3389/fphar.2019.00385

[99] Kornicka, K., Marycz, K., Marędziak, M., Tomaszewski, K.A. and Nicpoń, J. (2016) The Effects of the dna Methyltranfserases Inhibitor 5-Azacitidine on Ageing, Oxidative Stress and DNA Methylation of Adipose Derived Stem Cells. *Journal of Cellular and Molecular Medicine*, **21**, 387-401. https://doi.org/10.1111/jcmm.12972

[100] Derissen, E.J.B., Beijnen, J.H. and Schellens, J.H.M. (2013) Concise Drug Review: Azacitidine and Decitabine. *The Oncologist*, **18**, 619-624. https://doi.org/10.1634/theoncologist.2012-0465

[101] Cole, J.J., Robertson, N.A., Rather, M.I., Thomson, J.P., McBryan, T., Sproul, D., *et al.* (2017) Diverse Interventions That Extend Mouse Lifespan Suppress Shared Age-Associated Epigenetic Changes at Critical Gene Regulatory Regions. *Genome Biology*, **18**, Article No. 58. https://doi.org/10.1186/s13059-017-1185-3

[102] Conboy, I.M., Conboy, M.J., Wagers, A.J., Girma, E.R., Weissman, I.L. and Rando, T.A. (2005) Rejuvenation of Aged Progenitor Cells by Exposure to a Young Systemic Environment. *Nature*, **433**, 760-764. https://doi.org/10.1038/nature03260

[103] Martel, J., Ojcius, D.M., Wu, C., Peng, H., Voisin, L., Perfettini, J., *et al.* (2020) Emerging Use of Senolytics and Senomorphics against Aging and Chronic Diseases. *Medicinal Research Reviews*, **40**, 2114-2131. https://doi.org/10.1002/med.21702

[104] Horvath, S., Zhang, Y., Langfelder, P., Kahn, R.S., Boks, M.P., van Eijk, K., *et al.* (2012) Aging Effects on DNA Methylation Modules in Human Brain and Blood Tissue. *Genome Biology*, **13**, R97. https://doi.org/10.1186/gb-2012-13-10-r97

[105] Yücel, A.D. and Gladyshev, V.N. (2024) The Long and Winding Road of Reprogramming-Induced Rejuvenation. *Nature Communications*, **15**, Article No. 1941. https://doi.org/10.1038/s41467-024-46020-5

[106] Menon, S., Monteleon, C., Rhodes, A.S.J., Sebastiano, V. and Hsia, E. (2024) Transient Epigenetic Reprogramming: The Future of Skin Rejuvenation. *Dermatologic Surgery*, **50**, S145-S148. https://doi.org/10.1097/dss.0000000000004433