EPIGENETIC SKIN SCIENCE

Reverse the Skin Age Clock

Patented Skin Age Clock Technology & EPICELLINE®

STUDY OVERVIEW

FOREWORD

Looking young into old age is something many people dream of. By now, research shows that how we age is by no means predetermined. The appearance of our skin can be influenced by our lifestyle and environment.

The fascinating research area of “Epigenetics” reveals how this works: epigenetic mechanisms regulate the activity of our genes. We at Beiersdorf were the first to identify genome-wide epigenetic changes associated with skin aging, leading to the silencing of several skin-relevant genes. As a result, cells can’t function as they should, and they age.

The good news is that blocked and silenced genes can be reactivated, which means the appearance of the skin can be improved again. Beiersdorf is one of the pioneers in epigenetic skin research. Since 2008, an interdisciplinary team of 20 specialists has been investigating epigenetic changes in the skin as it ages. The goal: to use the individual epigenetic pattern to identify which blockages contribute to skin aging and how they can be resolved.

One of the key milestones in our epigenetic journey was the development of the first skin-specific age clock, an AI-based algorithm that uses the epigenetic pattern to objectively measure the biological age, i.e., the ‚true age‘ of the skin. To create this algorithm, we have analyzed skin samples from more than 1,000 people and measured 850,000 epigenetic data points per sample. This powerful tool then helped us to identify an active ingredient that fundamentally rejuvenates skin cells. Around 50,000 substances and extracts have now been scrutinized, and we have identified Epicelline®, the first active ingredient to turn back the age clock by restoring the youthful epigenetic pattern in aged skin cells, thus reactivating the silenced genes and improving skin cell functions, ultimately making the skin look younger than its chronological age.

This study book highlights some of our scientific publications on „Epigenetics and Skin Aging“, the „Patented Skin Age Clock Technology“, „Epicelline®“ and is a comprehensive overview to present the key take-home messages from the publications in a short, concise, and easy-to-understand manner.

Dr. Elke Grönniger
Epigenetics Lab Lead and
Inventor of Skin Age Clock
Technology & Epicelline®
Discovery

STUDY OVERVIEW
EPIGENETICS

OUR BREAKTHROUGH
EPIGENETIC INNOVATION

AGING IS AFFECTED **BY EPIGENETICS**

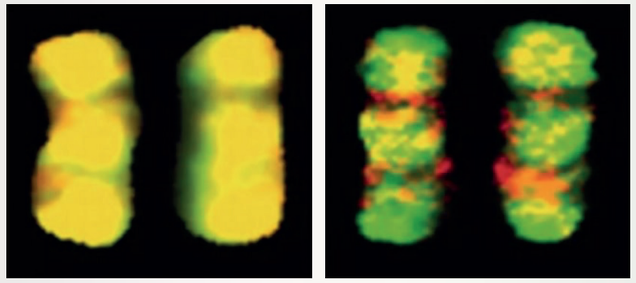
WHAT IS EPIGENETICS?

Epigenetics is the study of how lifestyle and environment can affect the way genes work.

Twins share the **same DNA**, but age **differently** due to their **lifestyles**

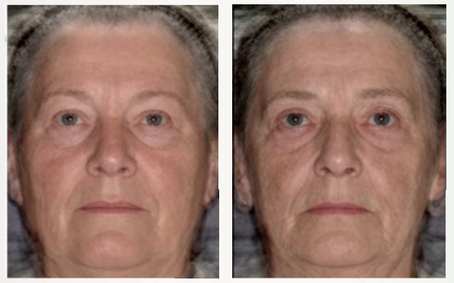
IDENTICAL TWINS START LIFE **WITH SIMILAR EPIGENOME**

Yellow regions indicate shared epigenetic tags[1]:



Chromosomes of **3 year** old identical twins

Chromosomes of **50 year** old identical twins



Same age, different expression, different signs of aging

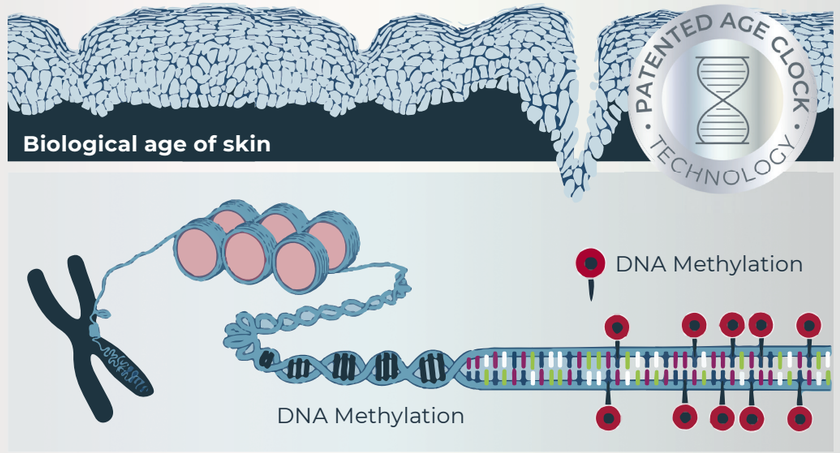
1 Fraga et al., Epigenetic differences arise during the lifetime of monozygotic twins. PNAS 2005
Christensen K et al., Perceived age as clinically useful biomarker of ageing: cohort study, 2009 (adapted)

Lifestyle and environmental factors influence how our DNA is epigenetically marked by a process called DNA methylation.

EPIGENETIC **SKIN SCIENCE**

EPIGENETICS & SKIN AGING

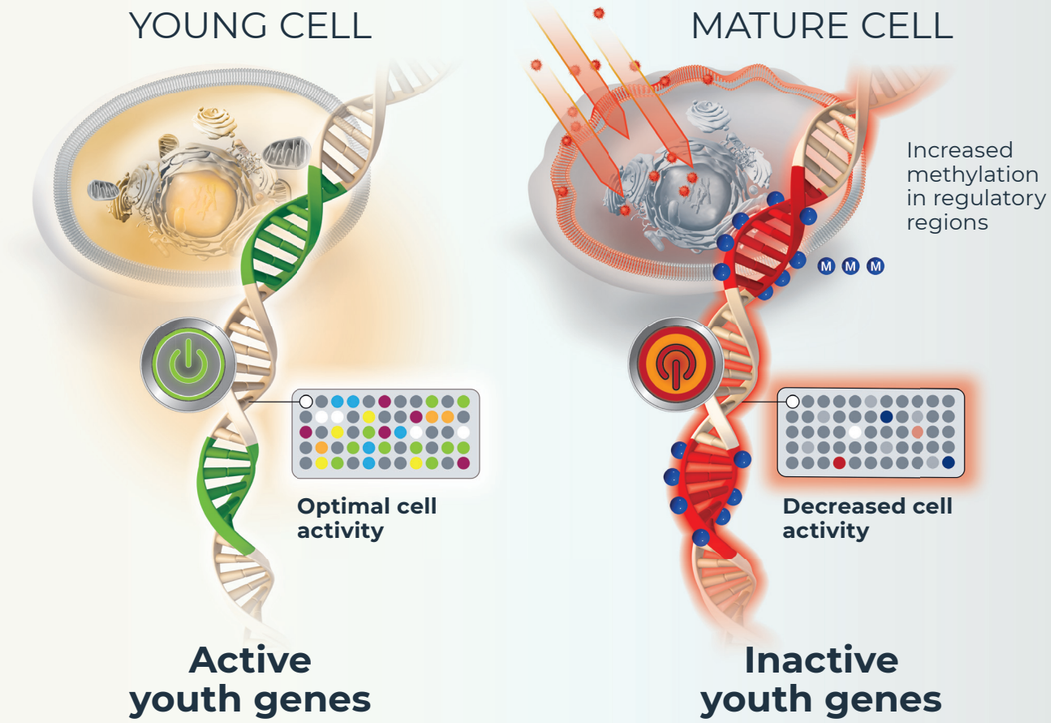
THE PROCESS OF **DNA METHYLATION**



Lifestyle and environmental factors

Skin aging is driven by lifestyle and environmental factors. Various factors, such as UV exposure, sports and nutrition are associated with altered DNA methylation patterns. This might cause an acceleration of biological skin aging, which is captured by DNA methylation clocks.

EPIGENETIC CHANGES **DRIVE AGING**



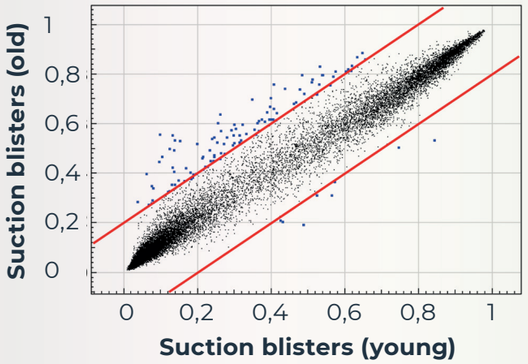
EPIGENETIC CHANGES **IN SKIN AGING IN 2010**

RESEARCH

Hypermethylation in regulatory gene regions upon skin aging

Aging and Chronic Sun Exposure Cause Distinct Epigenetic Changes in Human Skin

| Grönniger E, Weber B, Heil O, Peters N, Stäb F, Wenck H, Korn B, Winnefeld M, Lyko F



27.000 methylation sites were analyzed in suction blisters of young and old volunteers. Blue dots are significant differently methylated sites.
The graph shows the increased number of epigentic tags in the regulatory regions of genes in aged skin[2].

Epigenetic changes **upon skin aging** lead to **downregulation** of **youth genes**

2 Grönniger E et al. Aging and chronic sun exposure cause distinct epigenetic changes in human skin. PLoS Genet. 2010 May 27;6(5):e1000971. Raddatz G, et al. Aging is associated with highly defined epigenetic changes in the human epidermis. Epigenetics Chromatin. 2013 Oct 31;6(1):36.

PIONEERING EPIGENETIC RESEARCH **FOR OVER 15 YEARS**

Publication milestones

2010

>PLos Genet. 2010 May 27
Aging and Chronic Sun Exposure Cause Distinct Epigenetic Changes in Human Skin

HYPERMETHYLATION IN REGULATORY GENE REGIONS UPON SKIN AGING

2012

EPIGENETICS **IS THE MAIN DRIVER OF SKIN AGING**

>Genome Biol. 2012 Jul 30
The aging epigenome: DNA methylation from the cradle to

DNA METHYLATION PATTERNS CHANGE WITH INCREASING AGE AND SHOW STABLE ETHNIC VARIATIONS

>J Invest Dermatol. 2012 Feb
Stable ethnic variations in DNA methylation patterns of human skin

2013

>Epigenetics Chromatin. 2013 Oct 31
Aging is associated with highly defined epigenetic changes in the human epidermis

EPIGENETIC CHANGES UPON SKIN AGING LEAD TO DOWNREGULATION OF YOUTH GENES

2016

LOSS OF EPIGENETIC REGULATORY FIDELITY IS A KEY FEATURE OF THE AGING EPIGENOME

>Aging Cell. 2016 Jun 15
Reduced DNA methylation patterning and transcriptional connectivity define human skin aging

2020

>Aging (Albany NY). 2020 Jun 18
Multi-omics network analysis reveals distinct stages in the human aging progression in epidermal tissue

DNA METHYLATION AND TRASCRIPTOME SIGNATURES DEFINE EPIDERMAL RESPONSE TO ACUTE UV RADIATION

PATENTED AGE CLOCK · TECHNOLOGY ·

1ST SKIN SPECIFIC AGE CLOCK

2024

>xxx. 2024 Xnn 00
Development of an epigenetic clock to predict visual age progression of human skin

DEVELOPMENT OF **SKIN AGE CLOCK** TO PREDICT **VISUAL AGE**

2024

IDENTIFICATION OF EPICELLINE®

THE **1ST ACTIVE PROVEN TO #ReverseTheSkinAgeClock**

>Front Aging. 2024 Mar 4
Identification of dihydromyricetin as a natural DNA methylation inhibitor with rejuvenating activity in human skin

EPIGENETICS & SKIN AGING

PATENTED SKIN AGE CLOCK TECHNOLOGY

EPICELLINE®

EPIGENETICS & SKIN AGING

ORIGINAL WORK

AGING AND CHRONIC SUN EXPOSURE CAUSE DISTINCT EPIGENETIC CHANGES IN HUMAN SKIN

| Grönniger E, Weber B, Heil O, Peters N, Stäb F, Wenck H, Korn B, Winnefeld M, Lyko F
| PLoS Genet. 2010; 6(5): e10000971

Abstract:
Epigenetic changes are widely considered to play an important role in aging, but experimental evidence to support this hypothesis has been scarce. We have used array-based analysis to determine genome-scale DNA methylation patterns from human skin samples and to investigate the effects of aging, chronic sun exposure, and tissue variation. Our results revealed a high degree of tissue specificity in the methylation patterns and showed very little interindividual variation within tissues. Data stratification by age revealed that DNA from older individuals was characterized by a specific hypermethylation pattern. Interestingly, stratification by sun exposure produced a fundamentally different pattern with a significant trend towards hypomethylation. Our results thus identify defined age-related DNA methylation changes and suggest that these alterations might contribute to the phenotypic changes associated with skin aging.

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.1371%2Fjournal.pgen.1000971

The most important facts

QUESTION:

What are the effects of aging and chronic sun exposure on DNA methylation patterns?

ANSWER:

The effects of aging and chronic sun exposure on DNA methylation patterns in human skin samples were investigated using array-based analysis. Aging was associated with a specific hypermethylation pattern, while sun exposure shows a significant trend towards hypomethylation. The study suggests that epigenetic mechanisms may be functionally important for the phenotypic changes associated with aging.

ORIGINAL WORK

THE AGING EPIGENOME: DNA METHYLATION FROM THE CRADLE TO THE GRAVE

| Winnefeld M, Lyko F
| Genome Biol. 2012; 13(7): 165

Abstract:
Whole-genome methylation analysis of newborns and centenarians reveals widespread epigenetic alterations and provides new insight into age-related methylation pattern changes. There is growing evidence that epigenetic mechanisms play a crucial role in regulating a variety of biological processes, including aging. In addition to histone modifications, DNA methylation is a key epigenetic mechanism that controls gene expression and thereby alters cellular phenotypes. DNA methylation occurs at the carbon-5 position of cytosines located next to a guanosine (CpG dinucleotides). Although the total number of CpG dinucleotides is reduced in the human genome, CpG-rich sequences (CpG islands) are present and often located in promoter regions. More than half of all human genes harbor a CpG island, which is usually unmethylated. However, hypermethylation of specific CpG islands has been demonstrated in a wide range of biological conditions and shows a strong association with decreased gene expression. In addition, DNA methylation marks located outside of promoter regions (gene bodies, for example) can also regulate gene expression and are generating increasing interest. A recent publication has now shed new light on age-related epigenetic changes by studying the methylomes of a newborn and a centenarian.

LINK TO THE ORIGINAL PUBLICATION
The aging epigenome: DNA methylation from the cradle to the grave - PubMed (nih.gov)

The most important facts

QUESTION:

What are the key differences in DNA methylation patterns between a newborn and a centenarian, and how do these differences relate to age-related epigenetic changes?

ANSWER:

The main differences in DNA methylation patterns between newborns and centenarians are that the centenarian methylome shows pronounced hypermethylation in regulatory gene regions (in CpG island promoters), i.e. regulatory regions that have a strong influence on gene expression. In addition, the centenarian methylome exhibits pronounced hypomethylation compared to that of newborns, affecting approximately 500,000 CpG dinucleotides in CpG-depleted promoters and in genes that exhibit tissue-specific gene expression. These differences suggest that age-related epigenetic changes reflect an inefficient maintenance of methylation patterns which is a complex regulatory network of factors that influence genomic methylation patterns in different ways. Understanding these mechanisms could facilitate the development of specific intervention strategies.

ORIGINAL WORK

STABLE ETHNIC VARIATIONS IN DNA METHYLATION PATTERNS OF HUMAN SKIN

| Winnefeld M, Brueckner B, Grönniger E, Stäb F, Wenck H, Lyko F
| Journal of Investigative Dermatology 2012; 132(2): 466-468

Abstract:
We analyzed epigenetic variation in human skin samples from individuals of different ethnicities. We obtained epidermis samples from 30 healthy volunteers (10 Africans, 10 Asians, and 10 Caucasians) and analyzed DNA from all 30 samples using Illumina HumanMethylation27 BeadChip arrays to determine the methylation status of 27,578 CpG dinucleotides. Our analysis revealed that while there were only small differences in methylation patterns between individuals within an ethnicity, there were significant differences in methylation patterns between ethnicities. We identified a set of markers that were differentially methylated across all three ethnicities and showed that these markers were preferentially found at sites outside of CpG islands. Pathway analysis showed an enrichment in functional categories associated with dermatological diseases and conditions, consistent with known ethnic variations in skin function. Our data suggest that ethnic methylation differences affect only a small fraction of the genome but appear in many individuals from a specific ethnicity. This stability appears remarkable and distinguishes ethnic methylation differences from the stochastic epigenetic variation described in previous studies.

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.1038/jid.2011.323

The most important facts

QUESTION:

What is the degree of epigenetic heterogeneity among human individuals, and how does it compare to ethnic methylation differences?

ANSWER:

The degree of epigenetic heterogeneity among human individuals is a topic of considerable scientific debate. While it is widely assumed that environmental signals can modulate epigenetic marks to mediate phenotypic changes, the human epigenome appears to be relatively stable in differentiated cells. In contrast, ethnic methylation differences affect only a small fraction of the genome but appear in many individuals from a specific ethnicity, and these differences are stable and distinguishable from stochastic epigenetic variation. The stability of ethnic methylation differences can possibly be explained by the involvement of chromatin factors and/or genetic variations, which requires further investigation.

ORIGINAL WORK

AGING IS ASSOCIATED WITH HIGHLY DEFINED EPIGENETIC CHANGES IN THE HUMAN EPIDERMIS

| Raddatz G, Hagemann S, Aran D, Söhle J, Kulkarni P, Kaderali L, Hellman A, Winnefeld M, Lyko F
| Epigenetics Chromatin 2013; 6: 36

Background:
Altered DNA methylation patterns represent an attractive mechanism for understanding the phenotypic changes associated with human aging. Several studies have described global and complex age-related methylation changes, but their structural and functional significance has remained largely unclear.

Results:
We have used transcriptome sequencing to characterize age-related gene expression changes in the human epidermis. The results revealed a significant set of 75 differentially expressed genes with a strong functional relationship to skin homeostasis. We then used whole-genome bisulfite sequencing to identify age-related methylation changes at single-base resolution. Data analysis revealed no global aberrations, but rather highly localized methylation changes, particularly in promoter and enhancer regions that were associated with altered transcriptional activity.

Conclusions:
Our results suggest that the core developmental program of human skin is stably maintained through the aging process and that aging is associated with a limited destabilization of the epigenome at gene regulatory elements.

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.1186%2F1756-8935-6-36

The most important facts

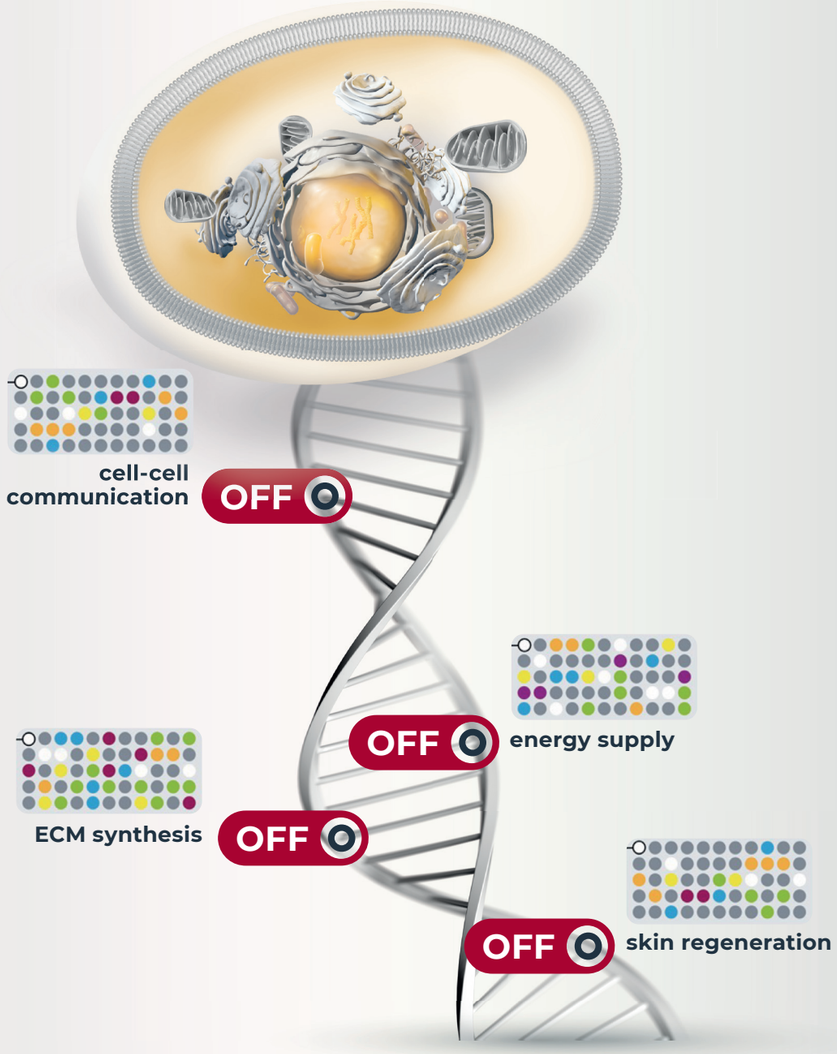
QUESTION:

Which impact do epigenetic changes have on skin aging?

ANSWER:

Epigenetic changes upon skin aging lead to a loss of function. The study revealed that epidermis methylomes showed age-related DNA methylation changes in gene regulatory regions.

EPIGENETICS & SKIN AGING



Deregulated genes contribute to several pathways

Aged keratinocytes can‘t act as they are supposed to

PATENTED AGE CLOCK **TECHNOLOGY**

THE 1ST **ACTIVE PROVEN TO #ReverseTheSkinAgeClock**

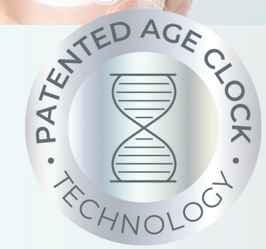
EPICELLINE®

1ST SKIN SPECIFIC AGE CLOCK **DEVELOPED BY EUCERIN**

SKIN SAMPLES

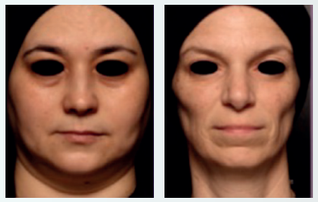
850,000 DATA POINTS ANALYSIS

PATENTED SKIN AGE CLOCK TECHNOLGY



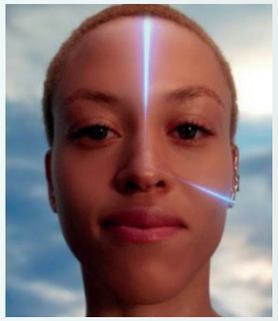
> Tool to measure biological SKIN AGE

SKIN CLOCK PREDICTS VISUAL AGE



44 years — 44 years — **> chron. age**
39 years — 55.5 years — **> visual age**

ACTIVE INGREDIENT SEARCH



2 Bormann F et al. Reduced DNA methylation patterning and transcriptional connectivity define human skin aging. Aging Cell. 2016 Jun;15(3
Bienkowska A et al, Development of an epigenetic clock to predict visual age progression of human skin. Front Aging. 2024 Jan 11;4:1258183.

AGE CLOCK **TECHNOLOGY**

- **15 YEARS OF RESEARCH**
- **INTERDISCIPLINARY TEAM OF 20 PEOPLE**
- **50.000 ACTIVE INGREDIENTS TESTED**

Our patented Skin Age Clock Technology is an algorithm based on the epigenetic patterns that allows our scientists to identify ingredients, which turn back time.

THE 1ST SKIN SPECIFIC AGE CLOCK

ORIGINAL WORK

REDUCED DNA METHYLATION PATTERNING AND TRANSCRIPTIONAL CONNECTIVITY DEFINE HUMAN SKIN AGING

| Bormann F, Rodríguez-Paredes M, Hagemann S, Manchanda H, Kristof B, Gutekunst J, Raddatz G, Haas R, Terstegen L, Wenck H, Kaderali L, Winnefeld M, Lyko F
| Aging Cell. 2016; 15(3): 563-571

Abstract:

Epigenetic changes represent an attractive mechanism for understanding the phenotypic changes associated with human aging. Age-related changes in DNA methylation at the genome scale have been termed 'epigenetic drift', but the defining features of this phenomenon remain to be established. Human epidermis represents an excellent model for understanding age-related epigenetic changes because of its substantial cell-type homogeneity and its well-known age-related phenotype. We have now generated and analyzed the currently largest set of human epidermis methylomes (N = 108) using array-based profiling of 450 000 methylation marks in various age groups. Data analysis confirmed that age-related methylation differences are locally restricted and characterized by relatively small effect sizes. Nevertheless, methylation data could be used to predict the chronological age of sample donors with high accuracy. We also identified discontinuous methylation changes as a novel feature of the aging methylome. Finally, our analysis uncovered an age-related erosion of DNA methylation patterns that is characterized by a reduced dynamic range and increased heterogeneity of global methylation patterns. These changes in methylation variability were accompanied by a reduced connectivity of transcriptional networks. Our findings thus define the loss of epigenetic regulatory fidelity as a key feature of the aging epigenome.

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.1111%2Facel.12470

PATENTED SKIN AGE CLOCK TECHNOLOGY

The most important facts

QUESTION:

What are the key features of age-related epigenetic changes in human skin?

ANSWER:

Age-related epigenetic changes in human skin include hypermethylation of CpG island and erosion of DNA methylation patterns which is characterized by a reduced variance within old methylomes and increased heterogeneity between old methylomes. These age-related erosion of methylation patterns is accompanied by a reduced fine-tuning in the transcriptional circuitry, possibly through methylation-dependent changes in transcription factor binding.

ORIGINAL WORK

MULTI-OMICS NETWORK ANALYSIS REVEALS DISTINCT STAGES IN THE HUMAN AGING PROGRESSION IN EPIDERMAL TISSUE

| Holzscheck N, Söhle J, Kristof B, Grönniger E, Gallinat S, Wenck H, Winnefeld M, Falckenhayn C, Kaderali L
| Impact Journal on Aging 2020; 12(12): 12393–12409

Abstract:
In recent years, reports of non-linear regulations in age- and longevity-associated biological processes have been accumulating. Inspired by methodological advances in precision medicine involving the integrative analysis of multi-omics data, we sought to investigate the potential of multi-omics integration to identify distinct stages in the aging progression from ex vivo human skin tissue. For this we generated transcriptome and methylome profiling data from suction blister lesions of female subjects between 21 and 76 years, which were integrated using a network fusion approach. Unsupervised cluster analysis on the combined network identified four distinct subgroupings exhibiting a significant age-association. As indicated by DNAm age analysis and Hallmark of Aging enrichment signals, the stages captured the biological aging state more clearly than a mere grouping by chronological age and could further be recovered in a longitudinal validation cohort with high stability. Characterization of the biological processes driving the phases using machine learning enabled a data-driven reconstruction of the order of Hallmark of Aging manifestation. Finally, we investigated non-linearities in the mid-life aging progression captured by the aging phases and identified a far-reaching non-linear increase in transcriptional noise in the pathway landscape in the transition from mid- to late-life.

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.18632%2Faging.103499

PATENTED SKIN AGE CLOCK TECHNOLOGY

The most important facts

QUESTION:

Can multi-omics integration be used to identify distinct stages in the aging progression from ex vivo human skin tissue?

ANSWER:

Yes, multi-omics integration can be used to identify distinct stages in the aging progression from ex vivo human skin tissue. The identified stages captured the biological aging state more clearly than a mere grouping by chronological age. The order of hallmark of aging manifestation throughout the aging phases was elucidated by applying a machine learning approach. This approach also led to the characterization of the phases regarding pathway importance, which subsequently revealed a distinctly non-linear decrease in pathway enrichment at the mid- to late-life transition.

ORIGINAL WORK

DEVELOPMENT OF AN EPIGENETIC CLOCK TO PREDICT VISUAL AGE PROGRESSION OF HUMAN SKIN

| Bienkowska A, Raddatz G, Söhle J, Kristof B, Völzke H, Gallinat S, Lyko F, Kaderali L, Winnefeld M, Grönniger E, Falckenhayn C
| Front. Aging 2024; 4:1258183

Abstract:
Aging is a complex process characterized by the gradual decline of physiological functions, leading to increased vulnerability to age-related diseases and reduced quality of life. Alterations in DNA methylation (DNAm) patterns have emerged as a fundamental characteristic of aged human skin, closely linked to the development of the well-known skin aging phenotype. These changes have been correlated with dysregulated gene expression and impaired tissue functionality. In particular, the skin, with its visible manifestations of aging, provides a unique model to study the aging process. Despite the importance of epigenetic age clocks in estimating biological age based on the correlation between methylation patterns and chronological age, a second-generation epigenetic age clock, which correlates DNAm patterns with a particular phenotype, specifically tailored to skin tissue is still lacking. In light of this gap, we aimed to develop a novel second-generation epigenetic age clock explicitly designed for skin tissue to facilitate a deeper understanding of the factors contributing to individual variations in age progression. To achieve this, we used methylation patterns from more than 370 female volunteers and developed the first skin-specific second-generation epigenetic age clock that accurately predicts the skin aging phenotype represented by wrinkle grade, visual facial age, and visual age progression, respectively. We then validated the performance of our clocks on independent datasets and demonstrated their broad applicability. In addition, we integrated gene expression and methylation data from independent studies to identify potential pathways contributing to skin age progression. Our results demonstrate that our epigenetic age clock, VisAgeX, specifically predicting visual age progression, not only captures known biological pathways associated with skin aging, but also adds novel pathways associated with skin aging.

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.3389%2Ffragi.2023.1258183

The most important facts

QUESTION:

What is the skin-specific epigenetic age clock VisAgeX?

ANSWER:

VisAgeX is an epigenetic age clock that is specifically designed for skin tissue. It uses DNA methylation patterns to accurately predict the visual age progression. The development of VisAgeX represents a significant advancement towards understanding the aging process and may serve as a basis for future investigations into the functional aspects influencing the speed of aging.

DISCOVERY OF EPICELLINE®

15 YEARS OF **RESEARCH**

50,000 INGREDIENTS **TESTED**

1 GROUNDBREAKING **INGREDIENT TO #REVERSETHEAGECLOCK**

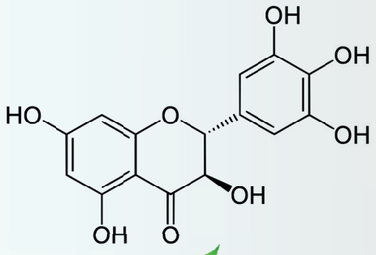
GROUNDBREAKING INGREDIENT **TO REVERSE THE AGE CLOCK**

EPICELLINE®

INCI: Dihydromyricetin (DHM) extracted from vine tea

Botanical source: Ampelopsis Grossedentata

Production: Ethanol Extraction



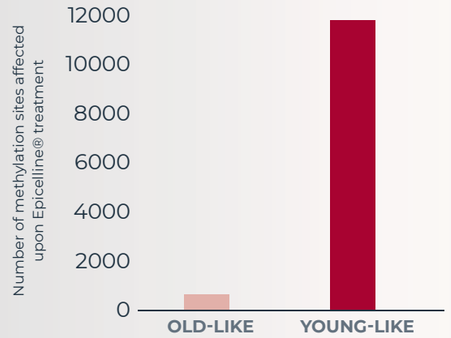
RAW MATERIAL SELECTION

The place of origin of the vine tea:
Jiangkou Country, Guizhou Province, China Zhangjiajie, Hunan Province, China

Use part:
Bud tips and young leaves

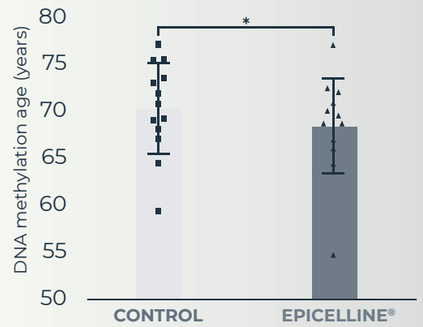
Harvesting method & processing technology:
Manual harvesting and natural drying, ethanolic extraction

EPICELLINE® reverses age-dependent DNA methylation changes and thus the skin SPECIFIC age clock IN VIVO.



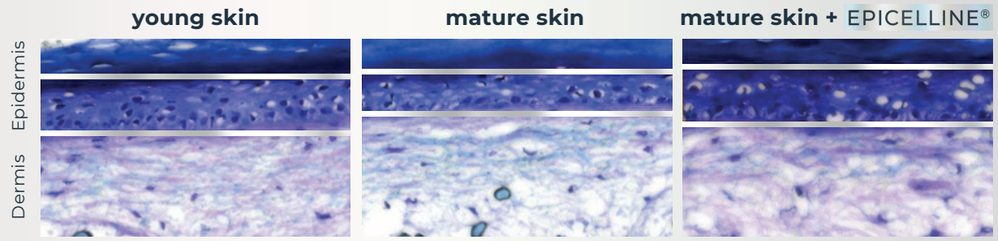
EPICELLINE® induces the DNA methylation pattern of the young epidermis[4]

EPICELLINE® restores the epigenetic youthful pattern and reduces the biological age of skin cells IN VITRO.



Reverses the Skin Age Clock[4]

EPICELLINE® increases the epidermis thickness.[3]



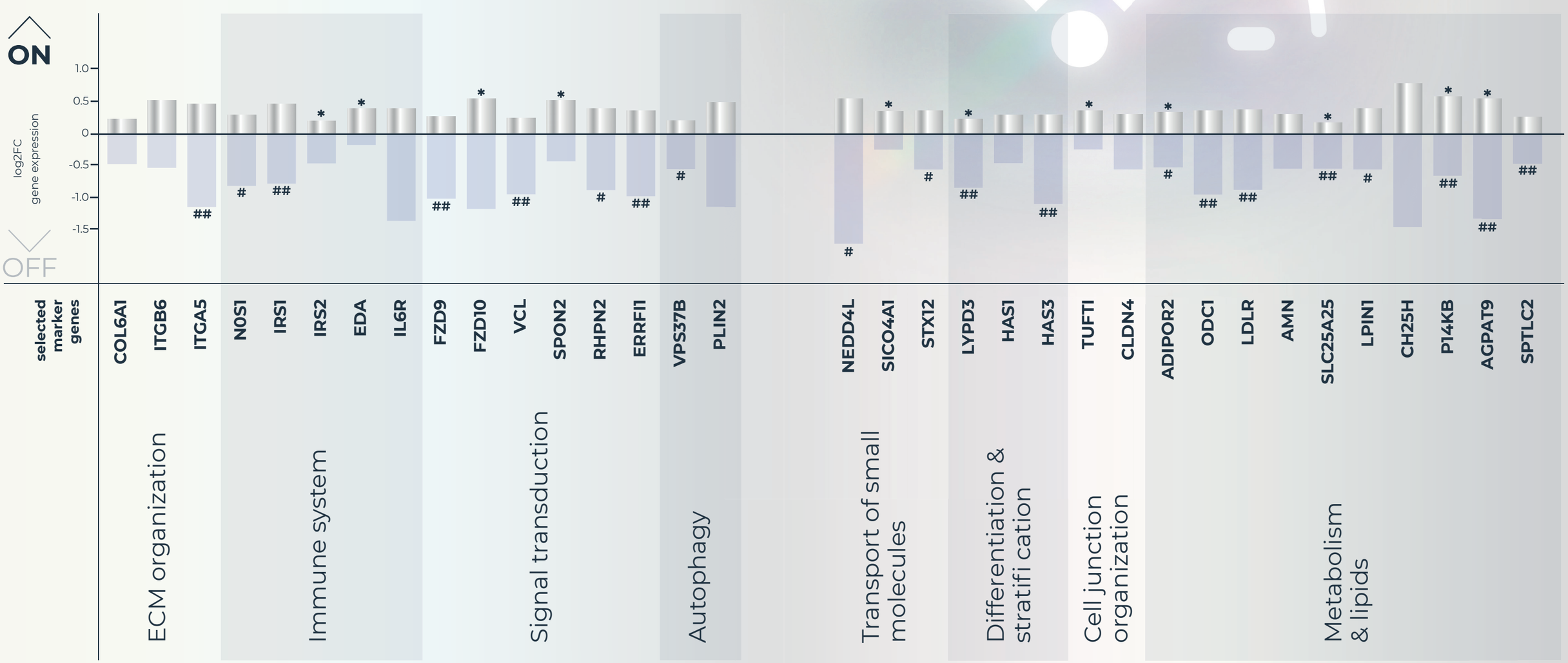
Skin equivalent has been treated with 20µM (=0.00064%) for 6 weeks

3 Improves the epidermal architecture and in creases the epidermal thickness (in vitro, 3D aging skin model). Skin equivalent has been treated with 20 µM DHM (=0.00064%) for 6 weeks. Falckenhayn C et al, Identification of dihydromyricetin as a natural DNA methylation inhibitor with rejuvenating activity in human skin. Front Aging. 2024 March

4 Falckenhayn C et al, Identification of dihydromyricetin as a natural DNA methylation inhibitor with rejuvenating activity in human skin. Front Aging. 2024 March

EPICELLINE®

EPICELLINE® REACTIVATES **SILENCED GENES** IN VIVO[5]



Topical EPICELLINE® treatment induces the **re-activation of selected marker genes** (silver bars) that are subject to age-related epigenetic silencing IN VIVO (grey bars).

Significant correlation of gene expression with in vivo wrinkle grade

being among the top 10% of genes correlated with in vivo wrinkle grade

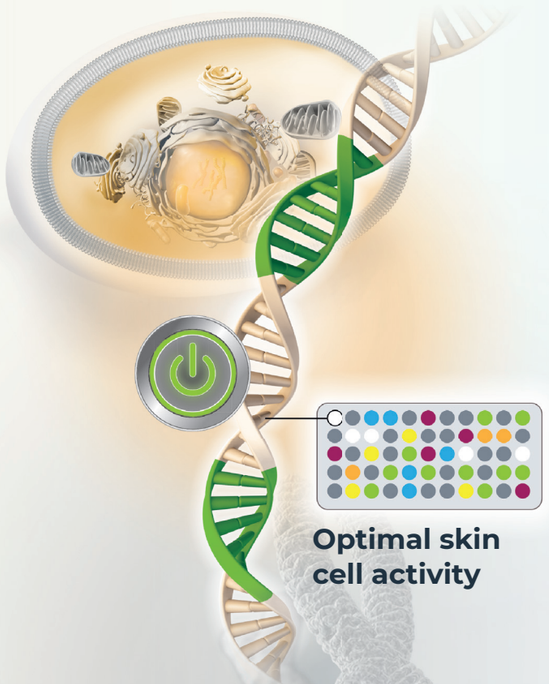
***** by Epicelline significantly up-regulated youth genes

5 Falckenhayn C et al, Identification of dihydromyricetin as a natural DNA methylation inhibitor with rejuvenating activity in human skin. Front Aging. 2024 March

EPIGENETIC **INNOVATION**

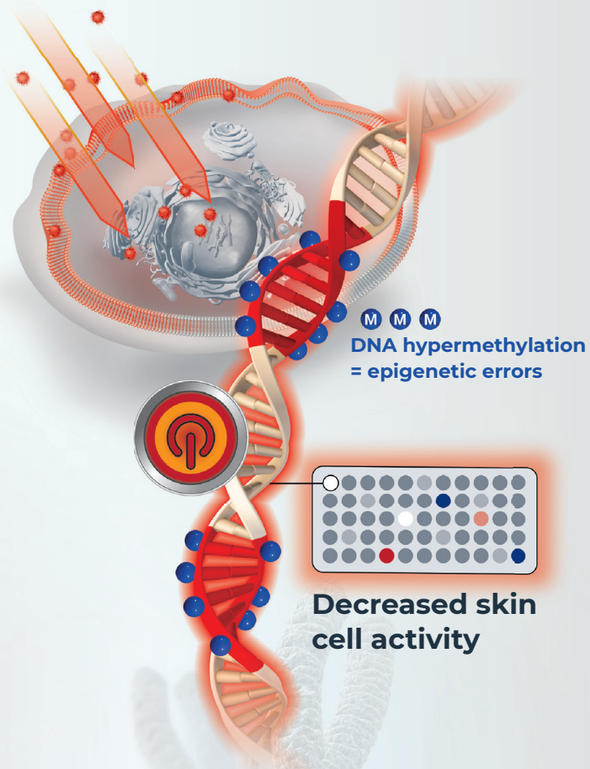
EPICELLINE®

Young skin cell



ACTIVE
youth genes

Mature skin cell



INACTIVE
youth genes

IS THE 1ST ACTIVE INGREDIENT PROVEN TO REVERSE THE AGE CLOCK

Re-activated youth genes by EPICELLINE®

✔ **Based on patented Age Clock Technology**

PATENTED AGE CLOCK · TECHNOLOGY ·

REACTIVATES
silenced genes

REVERSES
epigenetic changes

REJUVENATES
the skin cells

ORIGINAL WORK

IDENTIFICATION OF DIHYDROMYRICETIN AS A NATURAL DNA METHYLATION INHIBITOR WITH REJUVENATING ACTIVITY IN HUMAN SKIN

| Falckenhayn C, Bienkowska A, Söhle J, Wegner K, Raddatz G, Kristof B, Kuck D, Siegner R, Kaufmann R, Korn J, Baumann S, Lange D, Schepky A, Völzke H, Kaderali L, Winnefeld M, Lyko F, Grönniger E
| Front. Aging 2023; 4:1258184

Abstract:

Changes in DNA methylation patterning have been reported to be a key hallmark of aged human skin. The altered DNA methylation patterns are correlated with deregulated gene expression and impaired tissue functionality, leading to the well-known skin aging phenotype. Searching for small molecules, which correct the aged methylation pattern therefore represents a novel and attractive strategy for the identification of anti-aging compounds. DNMT1 maintains epigenetic information by copying methylation patterns from the parental (methylated) strand to the newly synthesized strand after DNA replication. We hypothesized that a modest inhibition of this process promotes the restoration of the ground-state epigenetic pattern, thereby inducing rejuvenating effects. In this study, we screened a library of 1800 natural substances and 640 FDA-approved drugs and identified the well-known antioxidant and anti-inflammatory molecule dihydromyricetin (DHM) as an inhibitor of the DNA methyltransferase DNMT1. DHM is the active ingredient of several plants with medicinal use and showed robust inhibition of DNMT1 in biochemical assays. We also analyzed the effect of DHM in cultivated keratinocytes by array-based methylation profiling and observed a moderate, but significant global hypomethylation effect upon treatment. To further characterize DHM-induced methylation changes, we used published DNA methylation clocks and newly established age predictors to demonstrate that the DHM-induced methylation change is associated with a reduction in the biological age of the cells. Further studies also revealed re-activation of age-dependently hypermethylated and silenced genes in vivo and a reduction in age-dependent epidermal thinning in a 3-dimensional skin model. Our findings thus establish DHM as an epigenetic inhibitor with rejuvenating effects for aged human skin.

EPICELLINE®

LINK TO THE ORIGINAL PUBLICATION
https://doi.org/10.3389%2Ffragi.2023.1258184

The most important facts

QUESTION:

Can Epicelline® serve as an anti-aging compound by restoring a youthful DNA methylation pattern in human skin cells?

ANSWER:

Yes, Epicelline® reduces the DNA methylation age in cultured primary human keratinocytes, which correlates with skin aging phenotypes, and induces a youthful DNA methylation pattern in vivo leading to the reactivation of age-related epigenetically silenced genes. Additionally, Epicelline® shows rejuvenating effects in 3-dimensional human skin models, indicating rejuvenating potential for cosmetical applications.

SCIENTIFIC POSTER

DIAGNOSTIC PROCEDURES

| Arrivabene F, Hagens R, Gallinger J, Jaspers S
| 33rd EADV Congress

Abstract:
Wrinkle AI is a fully automated system designed to analyze wrinkles extensively . It is the second part of a two-part process that involves collecting data using the PRIMOS CR Device. The device measures the topography of the eye corner area and removes the natural facial curvature using a proprietary high pass filter from Canfield‘s software.
Our studies vary from 20 to 100 volunteers, with 10 measurements per side per time point . All measurements are then converted to 3D point clouds and stored as DICOM files in an internal server. The Wrinkle AI analysis is started by the user via its web interface with one button click.
The analysis consists of three steps: data selection, registration, and measurement. In the data selection step, the system filters large amounts of data and selects the best subsets containing 2 to 4 images with the highest similarity among all timepoints. This is done to discard microvariations in mimic that could lead to wrong measurements, influencing eye wrinkle depth, length, and area.
In the registration step, the selected subsets go through a V-Net segmentation model to find all wrinkles and an „ID and Match“ module that instantiates each wrinkle. The subset is then registered based on the ID and Match data, where the image is only translated and rotated without warping to avoid changing the topographical information of the wrinkle
In the measurement step each wrinkle is measured using a reference surface created by our „Silk Cloth“ algorithm. The results contain all the information per wrinkle for each measurement. The system provides for distributional parameters (depth and width) the 90th percentile, mean, median, and maximum values to better explain the whole distribution of wrinkle parameters like width and depth. Other discrete parameters of the wrinkle are also given, such as area, length, skeleton length, and volume.

Wrinkle AI has the potential to provide valuable insights into the efficacy of wrinkle treatments and aid in the development of new products. It is a powerful tool for researchers and clinicians who are interested in understanding the underlying mechanisms of wrinkle formation and the effects of various treatments on wrinkle reduction.

The most important facts

QUESTION:

What is Wrinkle AI analysis and how does it work?

ANSWER:

Wrinkle AI is an automated system that analyzes the measured topography of wrinkles in the eye corner. The system provides detailed information about each wrinkle, including depth, width, area, length, skeleton length, and volume. The system is started by the user via its web interface with one button click and has the potential to provide valuable insights into the efficacy of wrinkle treatments.

SCIENTIFIC POSTER

REVERSE THE AGE CLOCK USING DIHYDROMYRICETIN (EPICELLINE®) TO REVERSE CLINICAL SIGNS OF AGING

| Warnke K, Plehn C, Djamil J, Borchers K, Muhr G, Kuhn A, Gallinger J, van Geloven A
| 33rd EADV Congress

Introduction & Objectives:
We investigated the capability of a new formulation with the epigenetic active Epicelline® to reverse multiple signs of aging for a younger-looking and rejuvenated skin in our in vivo studies. Epigenetic patterns encode skin's biological age, which we measured using AI-based age clocks. The active ingredient Epicelline® has been shown to reactivate skin's relevant genes, offering an innovative approach to anti-aging.

Materials & Methods:
We tested the product with 43 subjects for 4 weeks to assess signs of aging and conducted a tolerability study with 33 subjects for 2 weeks. We also conducted a user survey with 160 volunteers over 4 weeks to assess product performance.

Results:
The product significantly improved signs of aging after 4 weeks of use and was well-tolerated and highly suitable for all skin types. In a 4-week survey, a high percentage of consumers confirmed that signs of aging were reversed, skin aging visibly slowed down, and skin was rejuvenated, transformed, firmer, and younger-looking.

The most important facts

QUESTION:

What are the results of the in vivo studies investigating a new formulation with the epigenetic active Epicelline® for its capability to reverse 10 signs of aging?

ANSWER:

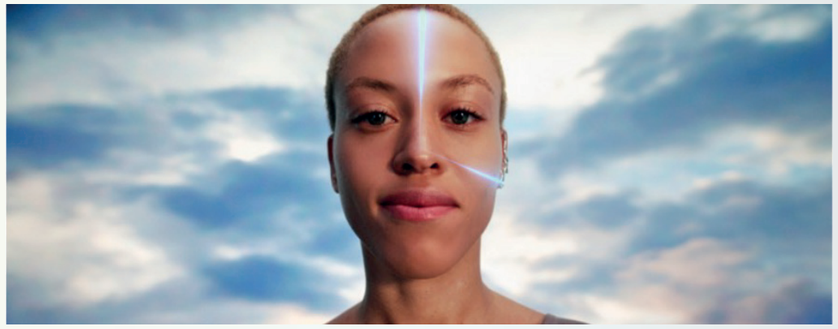
The clinical studies showed significant improvement in signs of aging such as lines, wrinkles, facial contours, firmness, and evenness, resulting in rejuvenated and younger-looking skin. The product was well-tolerated and highly suitable for all skin types, including sensitive skin. A user survey confirmed that signs of aging were reversed, skin aging visibly slowed down, and skin was firmer. The study suggests that optimizing epigenetic patterns offers an innovative approach to reverse signs of aging and turn back the age clock.

MAGAZINE ARTICLE

TURNING BACK THE SKIN‘S „AGE CLOCK“

| COSSMA Magazin, 10/2023
| Gunnar von der Geest

Summary:
Beiersdorf AG has been researching the epigenetics of skin aging for the last 15 years. Epigenetics is the link between external influences, such as nutrition, UV radiation, environmental pollution, and stress, and our genes. It determines the conditions under which certain genes are silenced and when they are reactivated, with no changes in the genetic information in the genome. Beiersdorf has analyzed more than 1,000 skin samples from subject groups and has gathered important knowledge about individual skin aging processes. The company has developed a Skin Age Clock technology that reads out the epigenetic patterns of skin samples, enabling age scientists to predict the biological age of the skin very precisely. They can also identify and select active ingredients and create product solutions that modulate the epigenetic pattern positively, with the ambition to not only slow down the aging processes but also turn back the biological clock and fundamentally rejuvenate skin cells. The Skin Age Clock technology is a milestone in anti-aging research for human skin and creates important conditions for measuring skin aging exactly and integrating active ingredients in creams that visibly rejuvenate the skin.



LINK TO THE ORIGINAL PUBLICATION
Turning back the skin‘s „age clock“: COSSMA

PATENTED SKIN AGE CLOCK TECHNOLOGY

MAGAZINE ARTICLE

BEIERSDORF’S PLANS TO TURN BACK THE AGE CLOCK: ‘EPIGENETICS IS NOT SET IN STONE’

| Cosmetics Business, 10/2023
| Julia Wray

Summary:
Beiersdorf has been researching epigenetics since 2008 and has recently received a patent for its Skin Age Clock technology. Epigenetics is the study of the interactions between environmental factors and DNA, and the Skin Age Clock technology is described as an “important milestone” in epigenetic anti-ageing research. The technology enables the detection of epigenetic patterns in skin samples, which can be used to predict the biological age of the skin. Beiersdorf scientists are confident that their epigenetics expertise will enable the creation of products that significantly change the way skin ages. The company is in a strong position asset-wise because it started early and has the knowledge and opportunity to screen actives with the powerful Age Clock. The challenge for the company will be to distil the science behind their upcoming discoveries into impactful and enticing promotion. The company is working with marketing and communications experts in-house to find the best way to translate the topic in an easy and understandable but also an exciting and interesting way. Beiersdorf believes that epigenetics will be the next “hot topic” in skin ageing and that it has a tool in hand to holistically address ageing processes.

LINK TO THE ORIGINAL PUBLICATION
How Beiersdorf is turning back time for skin ageing (cosmeticsdesign-europe.com)

Revolutionary Discovery in Skin Aging

EPIGENETICS IS THE MAIN DRIVER OF SKIN AGING

1ST SKIN SPECIFIC PATENTED AGE CLOCK TECHNOLOGY

EPICELLINE®

1ST ACTIVE PROVEN TO REVERSE THE AGE CLOCK

EPIGENETIC
SKIN SCIENCE

STUDY OVERVIEW

Beiersdorf

**Beiersdorf Aktiengesellschaft, Hamburg,
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