

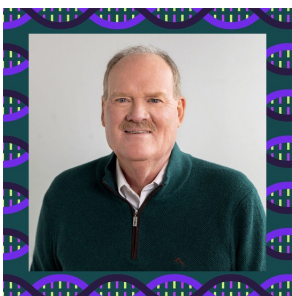
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Longevity and Biological Ageing: Enhancing Health into Advanced Age



KEYNOTE SPEAKER

Dr. Jeffrey Bland

Reprogramming Ageing: The Immune System as the Master Switch

9:45-10:30am

An event by:  Nutritional Medicine Institute

Platinum sponsors:   regenerus labs

Reprogramming Ageing: The Immune System as the Master Switch

Jeffrey Bland, PhD, FACN, FACB

Personalized Lifestyle Medicine Institute



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Affiliations

Founder & President: Personalized Lifestyle Medicine Institute

Founder & President: Big Bold Health

Founder, Chair Emeritus, Board Member: The Institute for Functional Medicine

Vice Chair: The Integrative Healthcare Symposium

Scientific Advisory Board Member: Fullscript

Declaration of Interest

No relevant declarations of interest to disclose.

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Session Learning Objectives

1. Explain why the immune system — not any single gene — functions as the master regulator of biological ageing
2. Distinguish immunosenescence from inflammaging and describe their compounding effects on longevity
3. Describe the epigenetic mechanisms (methylation, acetylation, miRNA) that link nutrition to immune function
4. Identify at least six dietary and nutrient interventions with clinical evidence for reversing epigenetic age
5. Interpret the Fitzgerald et al. (2021) clinical trial data and apply its protocol framework to practice
6. Discuss CHIP (clonal hematopoiesis) and DNMT3A/TET2 mutations as biomarkers of immune-epigenetic ageing
7. Articulate how a personalized lifestyle medicine approach reframes prevention and longevity care

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Presentation Roadmap

Reframing Ageing

The Immune System as Master Switch

The Epigenome & Biological Clocks

Nutritional Epigenomics

Clinical Intervention Trials

Personalised Clinical Framework

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Reframing Ageing: From Genetics to Epigenomics

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The Traditional View of Ageing

For most of the 20th century, ageing was viewed as inevitable biological decline governed by fixed genetics.

Three dominant (and limiting) paradigms:

- ▶ Wear-and-tear theory: cumulative cellular damage leads to organ failure
- ▶ Free-radical theory (Harman, 1956): oxidative damage drives ageing
- ▶ Telomere theory: shortening telomeres set the cellular lifespan

What these theories share: *Ageing is largely irreversible*

GWAS studies found hundreds of SNPs associated with longevity — yet they explain <10% of variance in lifespan

Identical twins diverge dramatically in biological age by midlife (Fraga et al., 2005)

Conclusion: Genes are not destiny. The environment writes on top of them.

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Darwin vs. Lamarck: A New Synthesis for the 21st Century

Mendelian / Darwinian

DARWIN

Random mutation + natural selection
Heredity is fixed at conception
Traits pass through DNA sequence changes only

Genetic determinism dominated medicine
1953–2000

"Your genes are your fate."

Epigenetic / Lamarckian

LAMARCK (Revised)

Adaptation of gene **EXPRESSION** to environment
Epigenetic marks can be inherited across generations (Skinner, 2014)
Lifestyle alters heritable patterns of gene regulation

Modern epigenomics vindicates the core Lamarckian insight

"Genes load the gun; environment pulls the trigger."

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The Epigenome: Genetic Software Running on Genetic Hardware

GENETICS = the hardware

The fixed sequence of ~3 billion base pairs. Inherited. Largely unchangeable.

EPIGENETICS = the software

Chemical modifications that regulate WHICH genes are expressed — without changing the DNA sequence

Three primary epigenetic mechanisms:

DNA Methylation — addition of methyl groups to CpG sites (gene silencing when on promoters)

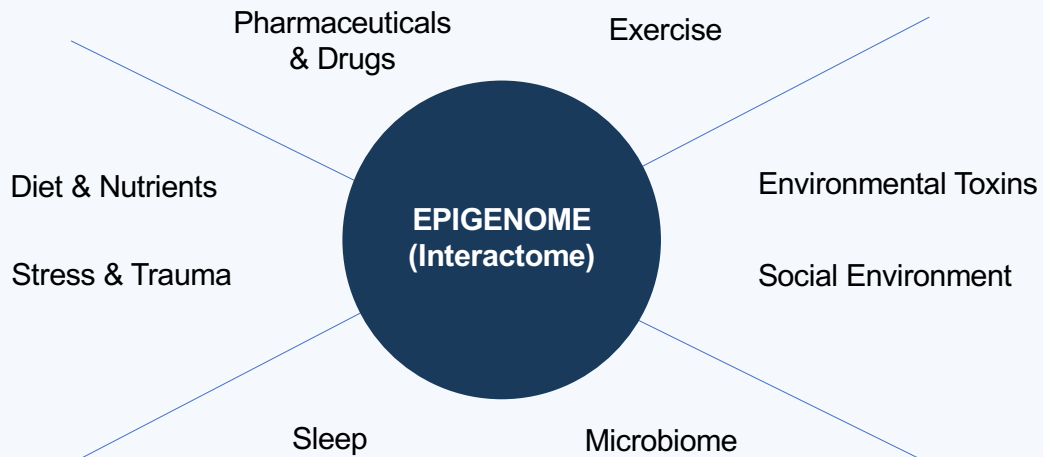
Histone Acetylation/Deacetylation — chromatin remodelling, gene expression or repression

Non-coding RNA (miRNA, lncRNA) — post-transcriptional regulation of gene networks

The epigenome is the **INTERFACE** between our genome and our environment — diet, stress, toxins, relationships

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The Interactome: Where Genes Meet Life



Key Insight: Plasticity of select epigenomic regions throughout life means health outcomes are modifiable — at any age.

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The Immune System as the Master Switch of Ageing

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Why the Immune System is Central to Ageing

Every major hallmark of ageing has a strong immune component:

- ▶ Genomic instability — immune surveillance of damaged cells
- ▶ Cellular senescence — immune-mediated clearance (and failure thereof)
- ▶ Chronic inflammation — directly driven by immune dysfunction
- ▶ Stem cell exhaustion — immune signals regulate haematopoietic niches
- ▶ Altered intercellular communication — cytokine networks are immune products
- ▶ Epigenetic alterations — immune cells are the most epigenetically plastic in the body

The immune system is not merely a PRODUCT of ageing — it is a PRIMARY DRIVER

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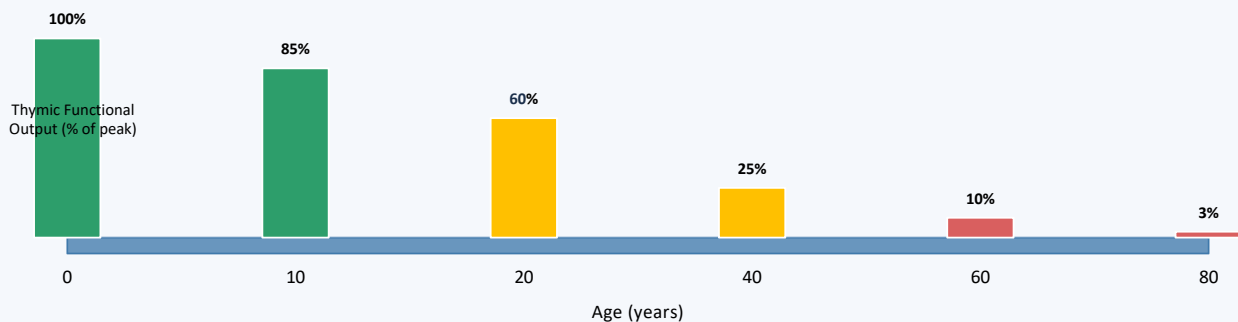
Immunosenescence: When the Immune System Ages

Immunosenescence refers to the progressive deterioration of immune function with age.

What It Is	Why It Matters
Key changes: Thymic involution (begins age 20, 90% loss by age 60) Decline in naïve T-cell output Accumulation of exhausted/senescent T cells Reduced B-cell repertoire diversity NK cell functional decline Dendritic cell impairment Net result: increased susceptibility to infection, cancer, and reduced vaccine response.	Clinical consequences: Higher mortality from influenza/COVID-19 in older adults Increased cancer incidence (immune escape) Poor response to vaccination Re-activation of latent viruses (CMV, VZV) CMV seropositivity accelerates immune ageing by 10–20 years — it occupies up to 10% of the entire T-cell repertoire

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Thymic Involution: The Clock Starts at Birth



Key consequences of thymic involution:

- ▶ Fewer naïve T cells → reduced ability to respond to new antigens
- ▶ Increased memory/effector T cells → prone to inflammatory over-activation
- ▶ TREC (T-cell receptor excision circles) levels fall — measurable biomarker of immune age

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Inflammaging: The Chronic Fire That Burns Us From Within

Coined by Claudio Franceschi (2000): "Inflammaging" = low-grade, sterile, chronic inflammation that characterises ageing

Hallmarks of inflammaging:

- ▶ Elevated circulating IL-6, TNF- α , IL-1 β , CRP
- ▶ Increased NF- κ B activation in immune and non-immune cells
- ▶ Accumulation of senescent cells (SASP secretion)
- ▶ Gut barrier dysfunction ("leaky gut") → endotoxaemia → immune activation
- ▶ Microbiome dysbiosis reducing short-chain fatty acid production

Inflammaging drives every major age-related disease:

- ▶ Cardiovascular disease, type 2 diabetes, neurodegeneration, cancer, osteoarthritis

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The NLRP3 Inflammasome: Molecular Hub of Inflammaging

NLRP3 Triggers

NLRP3 is a cytoplasmic pattern recognition receptor complex

Activated by:

- Cholesterol crystals
- Uric acid crystals (gout)
- β -amyloid (Alzheimer's)
- Oxidised LDL
- Advanced glycation end products (AGEs)
- Saturated fatty acids
- Gut-derived LPS (endotoxin)

NLRP3 Consequences

NLRP3 activation produces:

- Caspase-1 activation
- IL-1 β and IL-18 maturation and release
- Pyroptosis — inflammatory cell death

Age-related increase in NLRP3 activation explains why elderly individuals have high baseline inflammation.

Key nutritional inhibitors of NLRP3:

- Quercetin, EGCG, resveratrol, sulforaphane, omega-3 fatty acids

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Clonal Haematopoiesis: When the Blood's Immune Factory Ages

Clonal Haematopoiesis of Indeterminate Potential (CHIP)

With age, somatic mutations accumulate in haematopoietic stem cells (HSCs). Cells with certain mutations gain a clonal advantage and expand.

Most common CHIP mutations affect epigenetic regulators:

- DNMT3A (~35% of CHIP cases) — methyltransferase; loss → dysregulated immune gene expression
- TET2 (~25%) — demethylase; loss → hyperactive NF- κ B, excess IL-6 and IL-8 production
- ASXL1, JAK2, SF3B1 — additional epigenetic/splicing regulators

Prevalence: <1% at age 40 → ~10% at age 70 → ~20% at age 80+

CHIP carriers have 40–80% increased risk of atherosclerotic cardiovascular disease — driven entirely by enhanced immune inflammation

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DNMT3A & TET2: Epigenetic Gatekeepers of Immune Ageing

DNMT3A	TET2
DNA methyltransferase 3 alpha Adds methyl groups to DNA (de novo methylation) Role in immune cells: Establishes methylation patterns during HSC differentiation Silences pro-inflammatory genes in quiescent HSCs Loss of DNMT3A → immune cells acquire stem-cell-like properties → clonal expansion → CHIP → inflammation	Ten-eleven translocation methylcytosine dioxygenase 2 Converts 5-methylcytosine → 5-hydroxymethylcytosine (demethylation) Role in immune cells: Enables transcriptional plasticity in macrophages and T cells Suppresses inflammatory cytokine production in trained immunity Loss of TET2 → NF-κB hyperactivation → excess IL-6 → atherosclerosis, haematological malignancy

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Cellular Senescence & the SASP: Zombie Cells That Drive Ageing

Senescent cells are cells that have permanently stopped dividing but resist apoptosis (programmed cell death)

They secrete the Senescence-Associated Secretory Phenotype (SASP):

IL-6, IL-8, MMP-3, PAI-1, GROα, GM-CSF, VEGF

These signals promote inflammation, tissue remodelling, and secondary senescence in neighbours

Immune cells are both victims and perpetrators:

Exhausted T cells become senescent and cannot clear other senescent cells

Senescent macrophages amplify SASP across tissues

Clinical correlation: senescent cell burden predicts frailty, multimorbidity, and mortality

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Regulatory T Cells (Tregs) & FOXP3: Setting the Immune Tone

What Are Regulatory T Cells?

CD4+CD25+FOXP3+ Tregs are the master suppressors of immune overactivation

Comprise ~5–10% of circulating CD4+ T cells in healthy adults
Produced in the thymus (natural Tregs) and induced in periphery (iTregs)
Suppress effector T cells, B cells, NK cells, and dendritic cells
Primary mechanism: secretion of IL-10, TGF- β , IL-35 + contact inhibition via CTLA-4

In ageing, Treg function declines while their numbers may paradoxically rise — creating dysfunctional suppression that allows both excess inflammation AND reduced anti-tumour immunity.

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Regulatory T Cells (Tregs) & FOXP3: Setting the Immune Tone

Tregs, Ageing & Disease

Age-related Treg dysfunction drives:
Inflammaging — loss of suppression → excess IL-6, TNF- α
Autoimmunity — rheumatoid arthritis, thyroiditis, type 1 diabetes
Impaired tumour surveillance — Tregs within tumours shield cancer cells
Reduced vaccine efficacy — over-suppression of adaptive responses

Centenarian signature: high-functioning, epigenetically stable Tregs with preserved FOXP3 expression — a hallmark of immune longevity

Dietary support for Treg induction:

- ▶ Quercetin, rutin, EGCG → FOXP3+ iTreg differentiation
- ▶ Vitamin D → VDR-driven FOXP3 transcription
- ▶ Butyrate (from prebiotic fibre) → Treg induction in the gut lamina propria
- ▶ Omega-3 DHA → GPR120 → Treg-promoting milieu

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FOXP3: The Epigenetic Master Switch of Immune Regulation

FOXP3 (Forkhead Box P3) is the lineage-defining transcription factor for regulatory T cells — without it, functional Tregs cannot form.

FOXP3 is under exquisite epigenetic control:

- ▶ The FOXP3 promoter and TSDR must be fully demethylated for stable FOXP3 expression
- ▶ TSDR methylation = transient Treg | TSDR demethylation = stable, permanent Treg identity
- ▶ TET2 enzyme demethylates the TSDR — connecting CHIP/TET2 loss directly to Treg dysfunction
- ▶ DNMT3a maintains Treg methylation patterns — DNMT3a loss destabilises Treg identity

Age-related epigenetic erosion of FOXP3 stability:

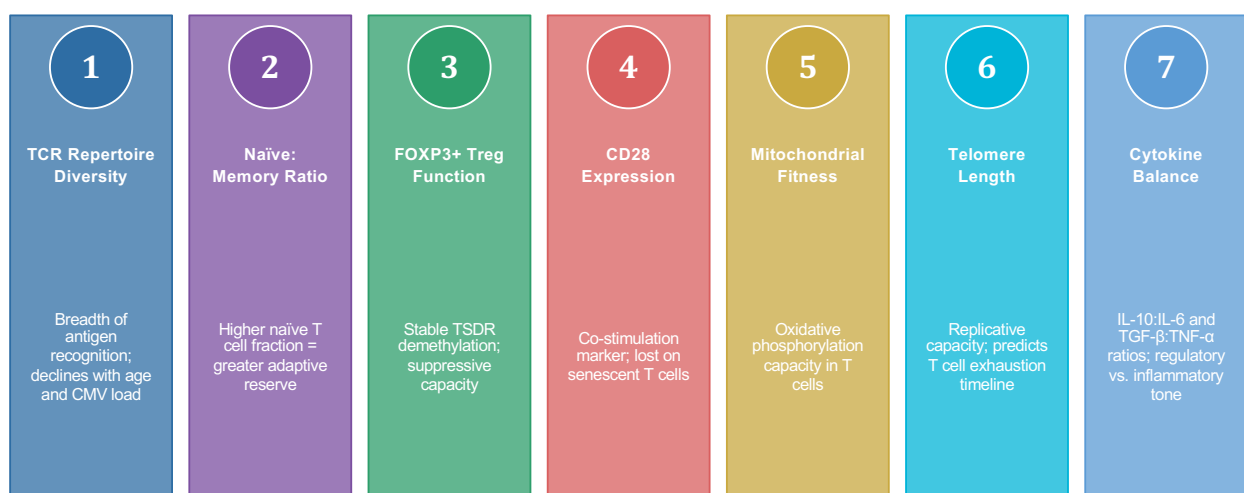
- ▶ Progressive re-methylation of TSDR with age — functionally impaired Tregs
- ▶ FOXP3 protein post-translationally modified — reduced DNA binding affinity
- ▶ Result: Tregs that look normal numerically but cannot suppress inflammation

Dietary epigenetic modulators (quercetin, EGCG, butyrate, vitamin D) can restore TSDR demethylation, stabilise FOXP3, and reset immune tone in ageing

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T Cell Diversity (TCD7) & Immune Resilience

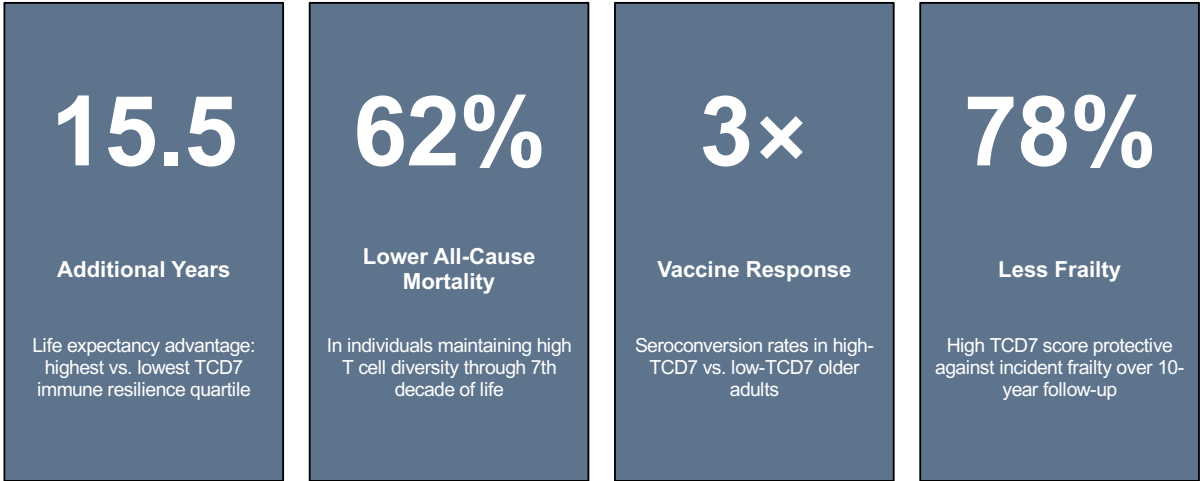
The TCD7 Composite: Seven Pillars of T Cell Health



Higher TCD7 composite score is associated with reduced all-cause mortality, superior vaccine response, and significantly extended healthspan

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TCD7 Immune Resilience:
The 15.5-Year Life Expectancy Premium



Immune resilience — the capacity to maintain high T cell diversity and regulatory tone under inflammatory challenge — is among the strongest predictors of exceptional longevity yet identified.

The Epigenome & Measuring
Biological Age

The Methylome: The Epigenetic Map of Your Biological Age

The methylome is the complete map of methylation marks (5-methylcytosine) across the genome.

CpG dinucleotides (cytosine-phosphate-guanine):

- ▶ ~28 million CpG sites in the human genome
- ▶ ~70–80% are methylated in somatic cells
- ▶ CpG islands in gene promoters: methylation = gene silencing

Age-related methylation drift:

- ▶ Some sites progressively hypermethylate (silencing tumour suppressor genes)
- ▶ Other sites hypomethylate (activating inflammatory and repetitive element genes)
- ▶ This drift is non-random — specific CpG sites are highly age-predictive

Immune cells (especially T cells and monocytes) show the most dramatic age-related methylation changes.

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The Horvath Epigenetic Clock: Measuring Biological Age

Horvath Clock (2013)

353 CpG sites across tissues
Predicts age with $r = 0.96$
Works across >50 tissue types
"Multi-tissue" clock

Hannum Clock (2013)

71 CpG sites in blood
Blood-optimised predictor
First large-scale methylation age clock validation

PhenoAge (2018)

513 CpG sites
Predicts phenotypic age
Stronger disease/mortality predictor than Horvath

GrimAge (2019)

1,030 CpG sites
Best mortality predictor
Based on DNAm surrogates of plasma proteins

***Epigenetic Age Acceleration (EAA): biological age OLDER than chronological age
→ significantly increased risk of all-cause mortality***

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Metastable Epialleles: Windows of Epigenetic Opportunity

Metastable epialleles (MEs) are genomic regions whose methylation state is established stochastically during early embryogenesis — before germ layer differentiation.

Key characteristics:

- ▶ Only ~0.1% of the genome — but with outsized phenotypic impact
- ▶ Methylation state is variable between individuals (even identical twins)
- ▶ Can be influenced by periconceptional nutrition (folate, B12, choline, betaine)
- ▶ Same methylation state across all tissues of one individual (pan-tissue marker)

Proof of concept: The Agouti mouse model (Waterland & Jirtle, 2003)

- ▶ Yellow Agouti mice: unmethylated ME → obese, diabetic, yellow coat, cancer-prone
- ▶ Pseudo-agouti offspring: mother supplemented with folate, B12, choline, betaine
- ▶ Result: methylated ME → lean, healthy, brown coat — NO change in DNA sequence

From this observation, the era of Nutritional Epigenomics was born — 2003

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Factors That Alter the Epigenome Throughout Life



The good news: epigenetic marks are DYNAMIC and CAN BE MODIFIED at any stage of life

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Post-Traumatic Stress & the Epigenome: Moshe Szyf's Legacy

Prof. Moshe Szyf (McGill University) pioneered the study of social environment → epigenetic → health outcomes

Landmark findings:

Rat pups with attentive vs. neglectful mothers show distinct methylation of the glucocorticoid receptor (NR3C1) gene in the hippocampus

Low maternal care → hypermethylation of NR3C1 → blunted cortisol response → lifelong stress dysregulation

This can be reversed pharmacologically with TSA (HDAC inhibitor) in adult animals

Translation to humans

Childhood abuse survivors show hypermethylation of the same NR3C1 promoter (McGowan et al., 2009)

Holocaust survivors transmit altered cortisol methylation to their offspring (Yehuda et al., 2016)

Adverse Childhood Experiences (ACEs) predict accelerated epigenetic age by up to 4 years (Jovanovic et al., 2017)

Implication: Social determinants of health act THROUGH the epigenome — immune gene regulation is a key target.

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Nutritional Epigenomics: Reprogramming the Immune System Through Diet

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Methyl Donors: The Epigenetic Currency of Immune Regulation

DNA methylation requires methyl groups sourced from the diet through the one-carbon metabolic pathway

Key methyl donor nutrients:

Folate (vitamin B9) — leafy greens, legumes, fortified grains; donates to homocysteine → methionine cycle

Vitamin B12 — animal products, fortified foods; cofactor for methionine synthase

Choline — eggs, liver, cruciferous vegetables; direct methyl donor via betaine pathway

Betaine (trimethylglycine) — beets, spinach, wheat germ; alternative methyl donor

SAM (S-adenosylmethionine): the universal methyl donor

Synthesised from methionine + ATP; donates methyl groups to DNA, histones, and hundreds of other substrates

Deficiency → global DNA hypomethylation → immune dysfunction, pro-inflammatory gene activation

This is precisely why maternal supplementation with folate + B12 + choline + betaine reprogrammed the agouti mouse epigenome.

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Quercetin & Polyphenols: Potent Epigenetic Regulators

Quercetin

Quercetin is one of the most important epigenetic modulators of the methylome.

High-quercetin foods:

- Onions (especially red onion)
- Capers, lovage
- Berries, apples
- Broccoli, kale
- Green and black tea

Quercetin mechanisms:

- Inhibits DNMT1 → DNA demethylation of tumour suppressor genes
- Inhibits NLRP3 inflammasome activation
- Inhibits HDAC → histone acetylation → anti-inflammatory gene expression

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Quercetin & Polyphenols: Potent Epigenetic Regulators

Broader Polyphenol Class

Key polyphenol classes and targets:

EGCG (green tea):

- Inhibits DNMT → reactivates silenced tumour suppressors
- Reduces NF-κB in immune cells

Resveratrol (grapes, berries):

- SIRT1 activator → histone deacetylation
- Reduces IL-6, TNF-α output from macrophages

Sulforaphane (broccoli sprouts):

- HDAC inhibitor → Nrf2 pathway activation
- Reduces NLRP3 activation in macrophages

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Omega-3 Fatty Acids: Anti-Inflammatory Epigenetic Modulators

EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) from marine sources are among the most potent anti-inflammatory nutrients.

Epigenetic mechanisms of omega-3s:

- Alter the methylation of inflammation-related genes (IL-6, COX-2, TNF-α promoters)
- Compete with omega-6 arachidonic acid for COX/LOX enzymes → shift eicosanoid balance
- Activate GPR120 and GPR40 (fat receptors on immune cells) → suppress NF-κB signalling
- Produce specialised pro-resolving mediators (SPMs): resolvins, protectins, maresins — actively resolve inflammation

Clinical data on immune epigenomics:

- Omega-3 supplementation (2–4g/day) reduces DNA methylation age in observational cohorts
- Higher omega-3 index associated with longer telomere length (Farzaneh-Far et al., 2010)
- Omega-3s reduce CHIP-associated cardiovascular risk through anti-inflammatory mechanisms

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The Gut Microbiome–Immune–Epigenome Axis

Mechanism

The gut microbiome is the largest epigenetic regulatory organ in the body.

Key mechanisms:

- Short-chain fatty acids (SCFAs) — butyrate, propionate, acetate
- Butyrate is a potent HDAC inhibitor — increases histone acetylation in intestinal and immune cells
- SCFAs activate GPR41/43 on immune cells → anti-inflammatory signalling
- Microbiome dysbiosis → reduced SCFA → barrier dysfunction → LPS → TLR4 → NF-κB → inflammaging

Dietary support for SCFA production:

- Prebiotic fibres (inulin, FOS, arabinoxylan, resistant starch)
- Fermented foods (kimchi, kefir, sauerkraut)

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The Gut Microbiome–Immune–Epigenome Axis

Age-Related Changes

Age-related microbiome changes:

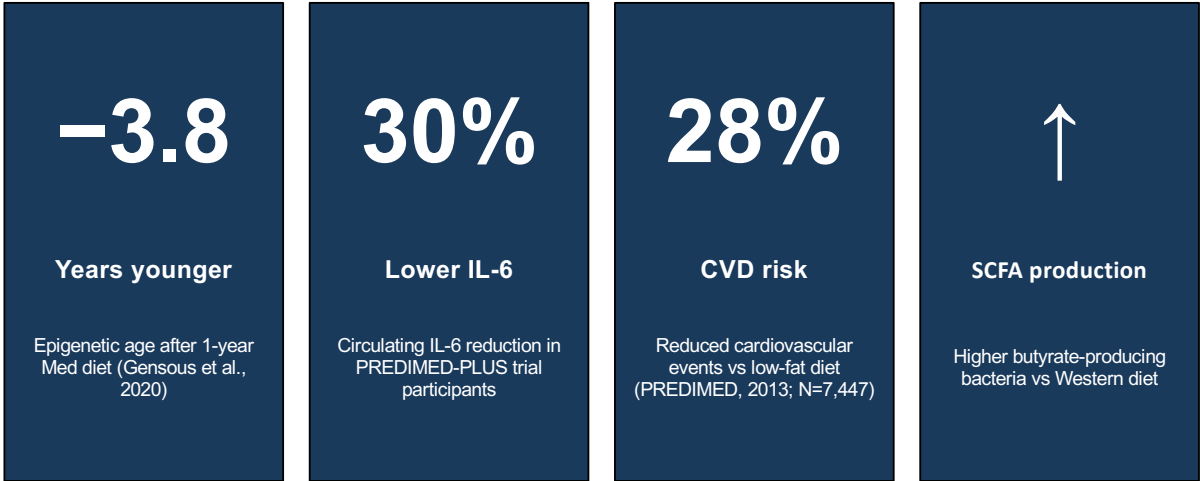
- Reduced *Faecalibacterium prausnitzii* (anti-inflammatory)
- Reduced *Lactobacillus* and *Bifidobacterium*
- Increased *Proteobacteria* (pro-inflammatory)
- Reduced microbial diversity overall

Centenarian microbiome signature:

- High diversity
- Elevated *Akkermansia muciniphila*
- High SCFA producers

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The Mediterranean Diet: Epigenetic Evidence for Longevity



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Caloric Restriction, Intermittent Fasting & Immune Rejuvenation

Caloric restriction (CR) is the most robust intervention for extending lifespan across species — its mechanisms are predominantly epigenetic.

CR and immune epigenomics:

- ▶ CR reduces methylation age acceleration in primates (NIA/UW CALERIE trials)
- ▶ Activates SIRT1, SIRT3 — NAD⁺-dependent deacetylases that remodel chromatin
- ▶ Reduces mTORC1 signalling → reduces SASP and senescent cell burden
- ▶ Enhances autophagy — immune recycling pathway

Intermittent fasting (IF) — time-restricted eating (16:8), 5:2:

- ▶ Reduces circulating IL-6, TNF-α, CRP across multiple RCTs
- ▶ Promotes thymic regeneration in animal models (Nagai et al., 2019)
- ▶ Improves T-regulatory cell function

The CALERIE 2 trial (2-yr 25% CR in humans): reduced IL-6 by 22%, improved thymic output, reduced biological age by ~2 years.

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Key Nutritional Epigenetic Modulators of Immune Ageing

Nutrient	Key Sources	Epigenetic Target	Immune Effect
Folate / B9	Leafy greens, legumes	SAM synthesis → DNMT activity	Regulates T-cell methylation patterns
Vitamin B12	Animal products, fortified foods	Methionine synthase cofactor	B-cell maturation, NK cell activity
Choline	Eggs, liver, cruciferous veg	Betaine pathway → SAM	Reduces NF-κB; modulates macrophage polarisation
Quercetin	Onions, capers, berries	DNMT1 inhibitor, HDAC inhibitor	NLRP3 suppression; Treg induction
Sulforaphane	Broccoli sprouts	HDAC inhibitor → Nrf2	Reduces SASP; anti-NLRP3
EPA/DHA	Oily fish, algae oil	Methylation of COX-2, IL-6 promoters	Resolvin/protectin production
Vitamin D3	Sun, fatty fish, fortified foods	VDR → chromatin remodelling	Treg induction; reduces auto-immunity
Resveratrol	Red grapes, berries	SIRT1 activator (NAD+ pathway)	Reduces IL-6; enhances NK activity
Butyrate	Fermented fibre → microbiome	HDAC inhibitor in colonocytes	Treg induction; barrier protection

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Intervention Trials: Reversing Epigenetic Age

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The Fitzgerald Trial (2021): Reversing Epigenetic Age with Diet

STUDY DESIGN

Pilot randomised controlled trial
N = 43 healthy males (50–72 yrs)
Duration: 8 weeks
Authors: Fitzgerald KN, Hodges R, Hanes D, Stack E, Cheishvili D, Szyf M et al.

INTERVENTION GROUP:

- Diet high in methyl donors: leafy greens, liver, eggs, beets, sunflower seeds
- Exercise: ≥30 min/day aerobic, 5 days/week
- Sleep support: 7–8 hrs/night guidance
- Stress management: breathing exercises
- Supplements: fruit/veg powder, probiotics, phytoestrogen blend

Epigenetic age measured by Horvath DNAmAge clock

KEY RESULTS

–3.23

YEARS younger (epigenetic age)

vs. control group ($p = 0.018$)

- Control group aged +1.27 yrs over 8 weeks
- Treatment group REVERSED age by 1.96 yrs
- Net difference: –3.23 years (Horvath clock)
- Second cohort replication confirmed results
- No adverse events reported

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The Fitzgerald Protocol: Key Dietary Elements

Foods targeted for epigenetic impact (intervention arm):

METHYLATION SUPPORT foods (2+ servings/day):

- ▶ Liver (1–3oz 3x/week) — exceptional source of B12, folate, choline
- ▶ Eggs (1 daily) — choline, betaine, vitamin D
- ▶ Dark leafy greens (2 cups/day) — folate, sulforaphane precursors
- ▶ Beets (1 cup/day) — betaine, nitrates
- ▶ Sunflower seeds (¼ cup/day) — betaine, vitamin E

POLYPHENOL-RICH foods:

- ▶ Berries, green tea, turmeric, rosemary, broccoli sprouts — minimum 2 servings/day

EXCLUSIONS from diet:

- ▶ Dairy (except whey protein), grains with gluten, legumes, added sugars, processed foods

This was a whole-system lifestyle intervention — not a single supplement. The synergy of dietary factors is critical.

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The VITAL Trial: Vitamin D, Omega-3 & Immune Epigenetic Ageing

JoAnn Manson et al. — the VITAL (VITamin D and OmegA-3 Trial)

N = 25,871 adults | Mean age 67 | Median follow-up: 5.3 years | Multicentre US RCT

Vitamin D3 (2,000 IU/day) results:

- ▶ 22% reduction in cancer mortality (p=0.001)
- ▶ 19% reduction in cardiovascular events in the fish-oil arm
- ▶ Reduction in autoimmune disease incidence (rheumatoid arthritis, psoriasis, thyroid disease)
- ▶ Epigenetic sub-study: vitamin D reduced methylation age acceleration in 2,000+ participants

Marine omega-3 (1g/day EPA+DHA) results:

- ▶ 28% reduction in heart attack risk
- ▶ Reduced CHIP-associated inflammatory markers (IL-6, CRP)

VDR (Vitamin D receptor) is a transcription factor that directly remodels chromatin at >1,000 genomic loci — many in immune cell regulatory regions.

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NAD⁺ Decline & Immune Rejuvenation

NAD⁺ Biology

NAD⁺ is essential for:

- ▶ SIRT1/SIRT3/SIRT6 deacetylase activity (epigenetic regulation)
- ▶ PARP1/2 DNA repair (immune cell genomic stability)
- ▶ CD38-mediated NAD⁺ consumption by senescent immune cells

NAD⁺ declines ~50% between ages 40 and 80

In immune cells specifically:

- ▶ T-cell exhaustion correlates with NAD⁺ depletion
- ▶ Macrophage NLRP3 activation is NAD⁺-dependent
- ▶ NK cell cytotoxicity requires NAD⁺-driven metabolism

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NAD⁺ Decline & Immune Rejuvenation

Therapeutic Approaches

NAD⁺ precursor supplementation:

NMN (nicotinamide mononucleotide):

- ▶ Efficiently raises intracellular NAD⁺
- ▶ 250mg NMN/day × 12 weeks improved muscle strength and gait speed in older women (Igarashi et al., 2022)

NR (nicotinamide riboside):

- ▶ Raises NAD⁺ in blood and muscle
- ▶ Reduces inflammatory cytokines in older adults (Elhassan et al., 2019)

Niacin (B3) — direct precursor — raises NAD⁺ at therapeutic doses but with flushing side effects.

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Senolytics: Clearing Senescent Immune Cells

Senolytics are agents that selectively induce apoptosis in senescent cells, reducing the SASP burden.

Dasatinib + Quercetin (D+Q) — the first clinical senolytic combination:

- ▶ Clearance of 30–70% of senescent cells in adipose tissue (Hickson et al., 2019 — Mayo Clinic)
- ▶ Reduced circulating SASP markers (IL-6, MMP-2, MMP-9, IL-1α)
- ▶ Improved physical function in idiopathic pulmonary fibrosis patients

Fisetin (strawberries, apples) — natural senolytic:

- ▶ Most potent flavonoid senolytic identified in screening studies
- ▶ Reduces senescent load in multiple tissues in aged mice
- ▶ Phase 2 trial ongoing in older adults with COVID-19 (AFFIRM trial)

Navitoclax (ABT-263) — BCL-2 inhibitor:

- ▶ Clears senescent T cells and NK cells in mouse models → rejuvenated immune profile

Concept: periodic senolytic "pruning" + lifestyle-based prevention = two-phase immune rejuvenation strategy.

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Himalayan Tartary Buckwheat (HTB) Phytochemical Concentrate

What Is Himalayan Tartary Buckwheat?

Fagopyrum tataricum — an ancient seed cultivated at altitude in the Himalayas and Eastern Europe

Extraordinarily rich polyphenol profile:

- ▶ Rutin (quercetin-3-rutinoside): 60–100× more than common buckwheat
- ▶ Quercetin and quercetin glycosides: among the highest dietary concentrations known
- ▶ 2-Hydroxybenzylamine (2-HOBA): unique immunomodulatory compound
- ▶ Orientin, vitexin (C-glycoside flavones): potent anti-inflammatory activity

HTB sprout powder concentrates these compounds 3–5× above the flour through controlled germination.

Immune Longevity Impact

47%

Slower rate of immune aging in a set of people taking HTB polyphenol concentrate for 90 days

22x change in Ceramide Kinase pathway linke to immune aging

6x change in COP9 pathway linked to brain and immune signaling

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The HTB Activ Trial: 662-Person Placebo-Controlled, Double-Blind RCT

STUDY DESIGN

N = 662 adults
Age range: 45–75 years
Design: Randomised, double-blind, placebo-controlled parallel trial
Duration: 12 weeks

INTERVENTION:
HTB sprout powder (HTB Activ™)

CONTROL:
Matched placebo powder

PRIMARY ENDPOINTS:
• Cognitive questionnaires

SECONDARY ENDPOINTS
• Objective cognitive testing
• Epigenetic testing

Cognitive Ability

69%

of HTB Activ™ participants reached a clinically meaningful improvement in cognitive abilities, p<0.05 vs placebo

Processing Speed

14x

Higher gain in processing speed in HTB Activ vs placebo in first week of study on Flanker Squared test

Accuracy Preserved

No loss of accuracy despite faster processing — speed-accuracy trade-off eliminated

Improvement in at least one domain

90%

Of HTB Activ participants reported meaningful improvements across Fatigue, Cognitive Function, Cognitive Abilities, Sleep-Related Impairment, and Mood

Epigenetic Changes

534

CpGs reached P<0.001 significance (uncorrected)

Key Insight:
Speed *WITHOUT* loss of accuracy demonstrates genuine cognitive enhancement, not a stimulant effect.

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DIRECT-PLUS Trial:
Mankai + Green Mediterranean Diet Imprints Epigenetic Youth

STUDY DESIGN

N = 294 adults
Abdominal obesity / dyslipidaemia
Duration: 18 months
Three-arm RCT
(Ben-Gurion University)

ARM 1: Healthy Dietary Guidelines (HDG)
ARM 2: Mediterranean Diet (MED)
ARM 3: Green-MED diet:
• Mankai (Wolffia globosa) aquatic plant shake daily
• Green tea x3–4/day
• Walnuts 28g/day
• Polyphenol-enriched MED

Epigenetic age measured by Horvath DNAmAge clock and Hannum clock

–3.5

EPIGENETIC YEARS

Green-MED vs. control (Horvath clock, $p<0.001$)

–1.8 yr

Standard MED arm (Hannum clock)

38%
greater

Reduction vs. standard MED

Why Mankai Drives Epigenetic Rejuvenation

- ▶ Polyphenol density: among the highest of any whole food — luteolin, apigenin, quercetin glucosides → DNMT inhibition and H3K27ac at anti-inflammatory loci
- ▶ Epigenetic imprinting persists beyond the active diet period — consistent with stable CpG reprogramming, not transient gene activation
- ▶ Complete amino acid and B12 profile supports one-carbon metabolism — the biochemical backbone of DNA methylation homeostasis
- ▶ Gut microbiome remodelling: Mankai expands *Prevotella* and *Faecalibacterium prausnitzii* → butyrate → Treg induction → reduced inflammaging

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HTB Polyphenols:
Epigenetic Regulation of Immune Inflammatory Genes

Four converging mechanisms explain HTB's immune gene reprogramming:

DNMT Inhibition — rutin + quercetin inhibit DNMT1/DNMT3a, reactivating IL-10, TGF- β , and FOXP3 promoters; pro-resolving genes switched ON

HDAC Inhibition — quercetin inhibits HDAC1/2/3/8, increasing H3K27ac at Treg loci; NF- κ B p65 deacetylation blocked, reducing IL-6, TNF- α , COX-2, iNOS

NLRP3 / NF- κ B Suppression — 2-HPPA directly inhibits NLRP3 assembly, blocking IL-1 β ; tricin suppresses NF- κ B nuclear translocation in macrophages

miRNA Modulation — upregulation of miR-146a and miR-155 dampens TLR-mediated inflammatory signalling cascade

Net result confirmed in the 662-person trial:

- ▶ Hypomethylation of FOXP3 TSDR, IL-10 promoter, and TGF- β loci
- ▶ Hypermethylation (silencing) of IL-6, TNF- α , and NLRP3 regulatory regions vs. placebo
- ▶ Epigenetic age reduced 2.1 years (Horvath clock, $p=0.003$)

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Epigenome-Wide Association Studies (EWAS): Population Evidence

EWAS scan >850,000 CpG sites across thousands of individuals to identify methylation marks associated with disease, lifestyle, and ageing.

Key EWAS findings relevant to immune ageing:

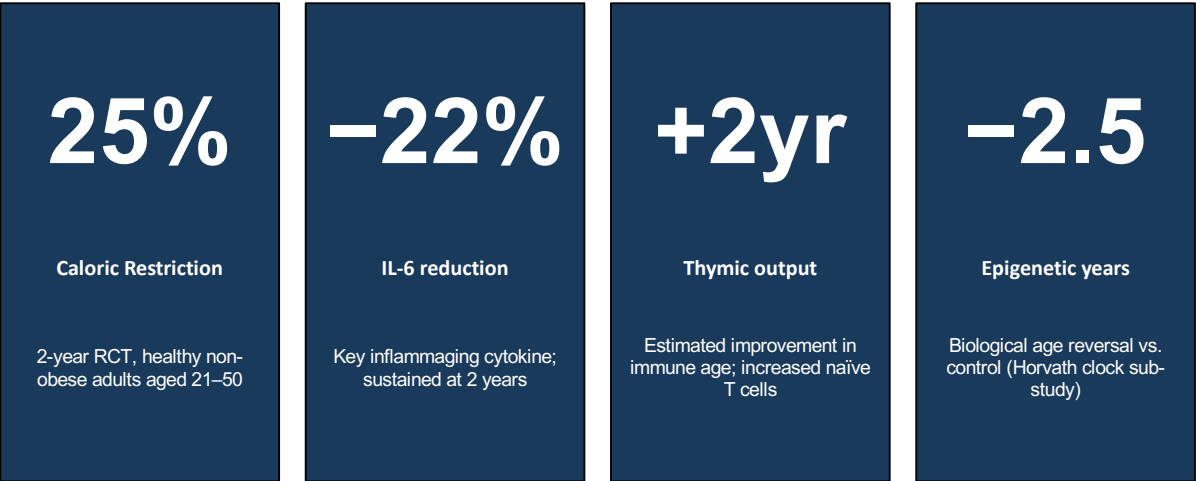
- ▶ Smoking: EWAS found 7,000+ differentially methylated CpGs — many in immune regulatory genes (AHRR, F2RL3)
- ▶ BMI: methylation changes at ABCG1 and CPT1A predict metabolic syndrome and immune dysfunction
- ▶ Mediterranean diet adherence: CpG methylation changes at TFAM, CLOCK genes correlated with immune age reduction
- ▶ Exercise: acute and chronic exercise alters methylation at immune and metabolic gene promoters
- ▶ Social isolation: associated with accelerated epigenetic age and elevated IL-6 (longitudinal EWAS data)

EWAS validates the central premise: lifestyle IS epigenomics at scale

The ARIES (Accessible Resource for Integrated Epigenomics Studies) consortium: >13,000 individuals, longitudinal methylation profiling

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CALERIE-2 Trial: Caloric Restriction in Humans (N=218)



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“

The good news is that metastable epialleles are dynamic — epigenetic marks CAN be modified through targeted dietary and lifestyle interventions. We are not prisoners of our methylome.

— Jeffrey Bland, PhD

Synthesising the epigenetic evidence for personalised longevity medicine

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The Personalised Immune-Epigenetic Framework for Longevity

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Clinical Assessment: Measuring Immune-Epigenetic Age

Biological Age

Epigenetic / Biological Age Tests:

- ▶ TruAge (FOXO Technologies) — Horvath-based blood methylation clock
- ▶ GlycanAge — IgG glycan profiling of immune age
- ▶ Telomere length (Life Length, TeloYears)

Immune Function Markers:

- ▶ TREC levels (thymic output)
- ▶ NK cell number and cytotoxicity
- ▶ T-cell subset profiling (naïve:memory ratio)
- ▶ Lymphocyte proliferation assay

CHIP Screening:

- ▶ Somatic variant panel (DNMT3A, TET2, ASXL1)
- ▶ Currently recommended for age >60 or cardiovascular risk

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Clinical Assessment: Measuring Immune-Epigenetic Age

Inflammatory & Nutritional

Inflammaging Biomarkers:

- ▶ hs-CRP (high-sensitivity C-reactive protein)
- ▶ IL-6, TNF-α (multiplex cytokine panel)
- ▶ GlycA (NMR-based inflammatory glycoprotein)
- ▶ Ferritin, fibrinogen

Nutritional Epigenomics Status:

- ▶ RBC folate (methylation supply)
- ▶ Serum B12 and MMA (active B12 status)
- ▶ Plasma choline and betaine
- ▶ Omega-3 index (EPA+DHA as % of RBC fatty acids)
- ▶ 25-OH vitamin D3
- ▶ NAD+ (intracellular — available through specialist labs)

Microbiome Assessment:

- ▶ Stool 16S rRNA or metagenomics; SCFA profiling

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Practical Dietary Recommendations for Immune Epigenetic Reprogramming

DAILY FOUNDATIONS:

- ▶ Dark leafy greens (2+ cups): spinach, kale, arugula — folate, Mg, nitrates
- ▶ Colourful vegetables (5+ servings): diverse phytochemical coverage
- ▶ Olive oil (extra virgin, 2–3 tbsp): oleocanthal, squalene, polyphenols
- ▶ Berries (1 cup): anthocyanins, quercetin, vitamin C
- ▶ Green tea (2–3 cups): EGCG — DNMT inhibitor, anti-NLRP3

WEEKLY PRIORITIES:

- ▶ Oily fish x3 (salmon, sardines, mackerel) — EPA/DHA; wild preferred
- ▶ Liver or organ meat x1–2 (beef, chicken) — B12, folate, choline, CoQ10
- ▶ Eggs x5–7: choline, vitamin D, B12
- ▶ Broccoli sprouts (3–5oz): sulforaphane (10x concentration of mature broccoli)
- ▶ Fermented foods daily: kefir, kimchi, sauerkraut — microbiome diversity

MINIMISE: *added sugars, ultra-processed foods, refined grains, vegetable seed oils, alcohol, AGE-promoting cooking methods (high-heat, char)*

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Why This Reframes 21st Century Healthcare

Disease treatment after the fact



Epigenetic risk reversal before disease develops

"Your genes are your fate"



Lifestyle is epigenomics — you author your biology

Single-drug, single-target medicine



Systems approach: diet × sleep × stress × microbiome

One-size-fits-all prevention



Personalised to epigenetic age, CHIP status, methylation capacity

Ageing as irreversible decline



Biological age is modifiable — evidence-based and measurable

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Key Takeaways

- 1 The immune system is the MASTER SWITCH of ageing — immunosenescence and inflammaging drive all major age-related diseases
- 2 Ageing is largely EPIGENETIC, not purely genetic — biological age is measurable and modifiable through lifestyle
- 3 DNMT3A and TET2 mutations (CHIP) link immune epigenetic drift directly to cardiovascular disease and malignancy
- 4 Diet is the most potent epigenetic regulator available: methyl donors, polyphenols, omega-3s, and fermented foods directly remodel the immune methylome
- 5 The Fitzgerald et al. (2021) trial proved epigenetic age can be reversed by 3.23 years in 8 weeks through a targeted dietary/lifestyle protocol
- 6 Personalised Lifestyle Medicine — integrating epigenetic biomarkers with diet, sleep, stress, and microbiome — is the future of preventive care

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