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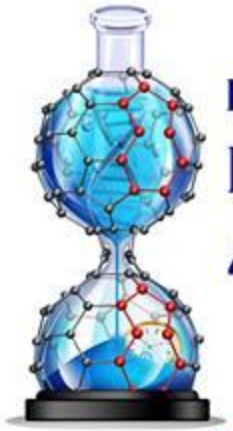
# Scientific News 1st of June 2014
# Sven Bulterijs

# Sven will be one of the speakers



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# Rejuvenation Biotechnology Conference 2014
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# Somatic mutations found in the healthy blood compartment of a 115-yr-old woman demonstrate oligoclonal hematopoiesis

The somatic mutation burden in healthy white blood cells (WBCs) is not well known. Based on deep whole-genome sequencing, we estimate that approximately 450 somatic mutations accumulated in the nonrepetitive genome within the healthy blood compartment of a 115-yr-old woman. The detected mutations appear to have been harmless passenger mutations: They were enriched in noncoding, AT-rich regions that are not evolutionarily conserved, and they were depleted for genomic elements where mutations might have favorable or adverse effects on cellular fitness, such as regions with actively transcribed genes. The distribution of variant allele frequencies of these mutations suggests that the majority of the peripheral white blood cells were offspring of two related hematopoietic stem cell (HSC) clones. Moreover, telomere lengths of the WBCs were significantly shorter than telomere lengths from other tissues. Together, this suggests that the finite lifespan of HSCs, rather than somatic mutation effects, may lead to hematopoietic clonal evolution at extreme ages.

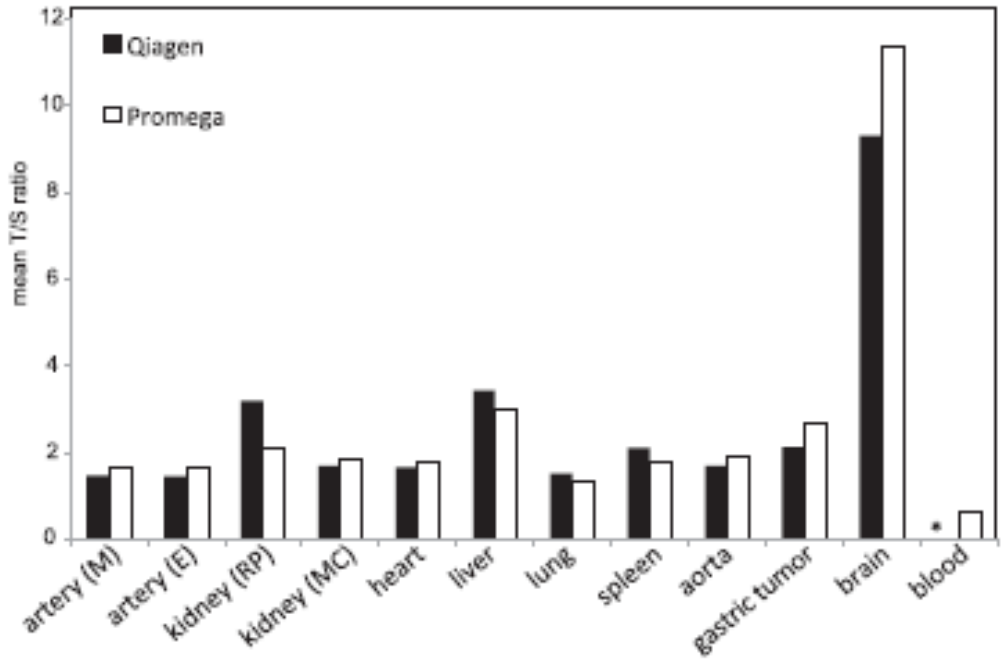


**Figure 1.** Mean telomere length of W115 tissues. DNA from W115

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# The metabolite α–ketoglutarate extends lifespan by inhibiting ATP synthase and TOR


Metabolism and ageing are intimately linked. Compared with *ad libitum* feeding, dietary restriction consistently extends lifespan and delays age-related diseases in evolutionarily diverse organisms[1,2]. Similar conditions of nutrient limitation and genetic or pharmacological perturbations of nutrient or energy metabolism also have longevity benefits[3,4]. Recently, several metabolites have been identified that modulate ageing[5,6]; however, the molecular mechanisms underlying this are largely undefined. Here we show that α-ketoglutarate (α-KG), a tricarboxylic acid cycle intermediate, extends the lifespan of adult *Caenorhabditis elegans*. ATP synthase subunit β is identified as a novel binding protein of α-KG using a small-molecule target identification strategy termed drug affinity responsive target stability (DARTS)[7]. The ATP synthase, also known as complex V of the mitochondrial electron transport chain, is the main cellular energy-generating machinery and is highly conserved throughout evolution[8,9]. Although complete loss of mitochondrial function is detrimental, partial suppression of the electron transport chain has been shown to extend *C. elegans* lifespan[10–13]. We show that α-KG inhibits ATP synthase and, similar to ATP synthase knockdown, inhibition by α-KG leads to reduced ATP content, decreased oxygen consumption, and increased autophagy in both *C. elegans* and mammalian cells. We provide evidence that the lifespan increase by α-KG requires ATP synthase subunit β and is dependent on target of rapamycin (TOR) downstream. Endogenous α-KG levels are increased on starvation and α-KG does not extend the lifespan of dietary-restricted animals, indicating that α-KG is a key metabolite that mediates longevity by dietary restriction. Our analyses uncover new molecular links between a common metabolite, a universal cellular energy generator and dietary restriction in the regulation of organismal lifespan, thus suggesting new strategies for the prevention and treatment of ageing and age-related diseases.

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# Resveratrol Levels and All-Cause Mortality in Older Community-Dwelling Adults


**IMPORTANCE** Resveratrol, a polyphenol found in grapes, red wine, chocolate, and certain berries and roots, is considered to have antioxidant, anti-inflammatory, and anticancer effects in humans and is related to longevity in some lower organisms.

**OBJECTIVE** To determine whether resveratrol levels achieved with diet are associated with inflammation, cancer, cardiovascular disease, and mortality in humans.

**DESIGN** Prospective cohort study, the Invecchiare in Chianti (InCHIANTI) Study ("Aging in the Chianti Region"), 1998 to 2009 conducted in 2 villages in the Chianti area in a population-based sample of 783 community-dwelling men and women 65 years or older.

**EXPOSURES** Twenty-four–hour urinary resveratrol metabolites.

**MAIN OUTCOMES AND MEASURES** Primary outcome measure was all-cause mortality. Secondary outcomes were markers of inflammation (serum C-reactive protein [CRP], interleukin [IL]-6, IL-1β, and tumor necrosis factor [TNF]) and prevalent and incident cancer and cardiovascular disease.

**RESULTS** Mean (95% CI) log total urinary resveratrol metabolite concentrations were 7.08 (6.69-7.48) nmol/g of creatinine. During 9 years of follow-up, 268 (34.3%) of the participants died. From the lowest to the highest quartile of baseline total urinary resveratrol metabolites, the proportion of participants who died from all causes was 34.4%, 31.6%, 33.5%, and 37.4%, respectively ($P$ = .67). Participants in the lowest quartile had a hazards ratio for mortality of 0.80 (95% CI, 0.54-1.17) compared with those in the highest quartile of total urinary resveratrol in a multivariable Cox proportional hazards model that adjusted for potential confounders. Resveratrol levels were not significantly associated with serum CRP, IL-6, IL-1β, TNF, prevalent or incident cardiovascular disease, or cancer.

**CONCLUSIONS AND RELEVANCE** In older community-dwelling adults, total urinary resveratrol metabolite concentration was not associated with inflammatory markers, cardiovascular disease, or cancer or predictive of all-cause mortality. Resveratrol levels achieved with a Western diet did not have a substantial influence on health status and mortality risk of the population in this study.

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# The Systemic Amyloid Precursor Transthyretin (TTR) Behaves as a Neuronal Stress Protein Regulated by HSF1 in SH-SY5Y Human Neuroblastoma Cells and APP23 Alzheimer's Disease Model Mice

**Xin Wang,[1] Francesca Cattaneo,[1,2] Lisa Ryno,[1] John Hulleman,[1] Natàlia Reixach,[1] and Joel N. Buxbaum[1]**

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Increased neuronal synthesis of transthyretin (TTR) may favorably impact on Alzheimer's disease (AD) because TTR has been shown to inhibit A$\beta$ aggregation and detoxify cell-damaging conformers. The mechanism whereby hippocampal and cortical neurons from AD patients and APP23 AD model mice produce more TTR is unknown. We now show that *TTR* expression in SH-SY5Y human neuroblastoma cells, primary hippocampal neurons and the hippocampus of APP23 mice, is significantly enhanced by heat shock factor 1 (HSF1). Chromatin immunoprecipitation (ChIP) assays demonstrated occupation of *TTR* promoter heat shock elements by HSF1 in APP23 hippocampi, primary murine hippocampal neurons, and SH-SY5Y cells, but not in mouse liver, cultured human hepatoma (HepG2) cells, or AC16 cultured human cardiomyocytes. Treating SH-SY5Y human neuroblastoma cells with heat shock or the HSF1 stimulator celastrol increased *TTR* transcription in parallel with that of *HSP40*, *HSP70*, and *HSP90*. With both treatments, ChIP showed increased occupancy of heat shock elements in the *TTR* promoter by HSF1. *In vivo* celastrol increased the HSF1 ChIP signal in hippocampus but not in liver. Transfection of a human *HSF1* construct into SH-SY5Y cells increased *TTR* transcription and protein production, which could be blocked by shHSF1 antisense. The effect is neuron specific. In cultured HepG2 cells, HSF1 was either suppressive or had no effect on TTR expression confirming the differential effects of HSF1 on *TTR* transcription in different cell types.

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# Identification of autophagy as a longevity-assurance mechanism in the aging model *Podospora anserina*

Laura Knuppertz,[1] Andrea Hamann,[1] Francesco Pampaloni,[2] Ernst Stelzer,[2] and Heinz D Osiewacz[1,*]

The filamentous ascomycete *Podospora anserina* is a well-established aging model in which a variety of different pathways, including those involved in the control of respiration, ROS generation and scavenging, DNA maintenance, proteostasis, mitochondrial dynamics, and programmed cell death have previously been demonstrated to affect aging and life span. Here we address a potential role of autophagy. We provide data demonstrating high basal autophagy levels even in strains cultivated under noninduced conditions. By monitoring an N-terminal fusion of EGFP to the fungal LC3 homolog PaATG8 over the lifetime of the fungus on medium with and without nitrogen supplementation, respectively, we identified a significant increase of GFP puncta in older and in nitrogen-starved cultures suggesting an induction of autophagy during aging. This conclusion is supported by the demonstration of an age-related and autophagy-dependent degradation of a PaSOD1-GFP reporter protein. The deletion of *Paatg1*, which leads to the lack of the PaATG1 serine/threonine kinase active in early stages of autophagy induction, impairs ascospore germination and development and shortens life span. Under nitrogen-depleted conditions, life span of the wild type is increased almost 4-fold. In contrast, this effect is annihilated in the *Paatg1* deletion strain, suggesting that the ability to induce autophagy is beneficial for this fungus. Collectively, our data identify autophagy as a longevity-assurance mechanism in *P. anserina* and as another surveillance pathway in the complex network of pathways affecting aging and development. These findings provide perspectives for the elucidation of the mechanisms involved in the regulation of individual pathways and their interactions.

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PLOS ONE

# Shorter Men Live Longer: Association of Height with Longevity and *FOXO3* Genotype in American Men of Japanese Ancestry

## Abstract

***Objectives:*** To determine the relation between height, *FOXO3* genotype and age of death in humans.

***Methods:*** Observational study of 8,003 American men of Japanese ancestry from the Honolulu Heart Program/Honolulu-Asia Aging Study (HHP/HAAS), a genetically and culturally homogeneous cohort followed for over 40 years. A Cox regression model with age as the time scale, stratified by year of birth, was used to estimate the effect of baseline height on mortality during follow-up. An analysis of height and longevity-associated variants of the key regulatory gene in the insulin/IGF-1 signaling (IIS) pathway, *FOXO3*, was performed in a HHP-HAAS subpopulation. A study of fasting insulin level and height was conducted in another HHP-HAAS subpopulation.

***Results:*** A positive association was found between baseline height and all-cause mortality (RR = 1.007; 95% CI 1.003–1.011; $P = 0.002$) over the follow-up period. Adjustments for possible confounding variables reduced this association only slightly (RR = 1.006; 95% CI 1.002–1.010; $P = 0.007$). In addition, height was positively associated with all cancer mortality and mortality from cancer unrelated to smoking. A Cox regression model with time-dependent covariates showed that relative risk for baseline height on mortality increased as the population aged. Comparison of genotypes of a longevity-associated single nucleotide polymorphism in *FOXO3* showed that the longevity allele was inversely associated with height. This finding was consistent with prior findings in model organisms of aging. Height was also positively associated with fasting blood insulin level, a risk factor for mortality. Regression analysis of fasting insulin level (mIU/L) on height (cm) adjusting for the age both data were collected yielded a regression coefficient of 0.26 (95% CI 0.10–0.42; $P = 0.001$).

***Conclusion:*** Height in mid-life is positively associated with mortality, with shorter stature predicting longer lifespan. Height was, moreover, associated with fasting insulin level and the longevity genotype of *FOXO3*, consistent with a mechanistic role for the IIS pathway.

# Reviews

Review

# Mutations that affect mitochondrial functions and their association with neurodegenerative diseases

Varinderpal S. Dhillon [a,b,*], Michael Fenech [a,b]

ABSTRACT

Mitochondria are essential for mammalian and human cell function as they generate ATP via aerobic respiration. The proteins required in the electron transport chain are mainly encoded by the circular mitochondrial genome but other essential mitochondrial proteins such as DNA repair genes, are coded in the nuclear genome and require transport into the mitochondria. In this review we summarize current knowledge on the association of point mutations and deletions in the mitochondrial genome that are detrimental to mitochondrial function and are associated with accelerated ageing and neurological disorders including Alzheimer's, Parkinson's, Huntington's and Amyotrophic lateral sclerosis (ALS). Mutations in the nuclear encoded genes that disrupt mitochondrial functions are also discussed. It is evident that a greater understanding of the causes of mutations that adversely affect mitochondrial metabolism is required to develop preventive measures against accelerated ageing and neurological disorders caused by mitochondrial dysfunction.

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JCB: Review

Cell biology of disease

# Telomeropathies: An emerging spectrum disorder

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A constellation of related genetic diseases are caused by defects in the telomere maintenance machinery. These disorders, often referred to as telomeropathies, share symptoms and molecular mechanisms, and mounting evidence indicates they are points along a spectrum of disease. Several new causes of these disorders have been recently discovered, and a number of related syndromes may be unrecognized telomeropathies. Progress in the clinical understanding of telomeropathies has in turn driven progress in the basic science of telomere biology. In addition, the pattern of genetic anticipation in some telomeropathies generates thought-provoking questions about the way telomere length impacts the course of these diseases.

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# Self-eating in the plaque: what macrophage autophagy reveals about atherosclerosis

Autophagy (or 'self-eating') is the process by which cellular contents are recycled to support downstream metabolism. An explosion in research in the past decade has implicated its role in both health and disease and established the importance of the autophagic response during periods of stress and nutrient deprivation. Atherosclerosis is a state where chronic exposure to cellular stressors promotes disease progression, and alterations in autophagy are predicted to be consequential. Recent reports linking macrophage autophagy to lipid metabolism, blunted inflammatory signaling, and an overall suppression of proatherogenic processes support this notion. We review these data and provide a framework for understanding the role of macrophage autophagy in the pathogenesis of atherosclerosis, one of the most formidable diseases of our time.