



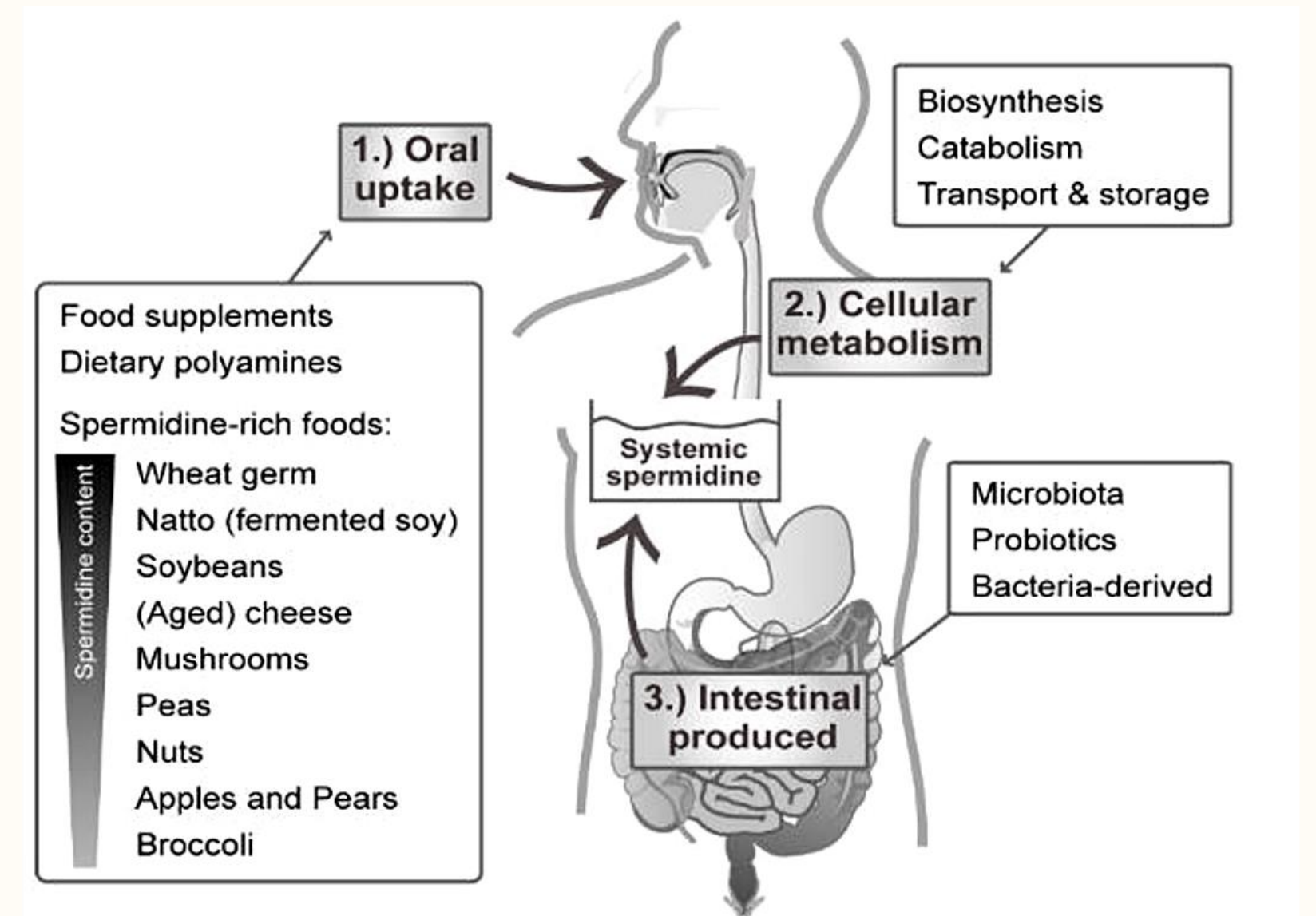
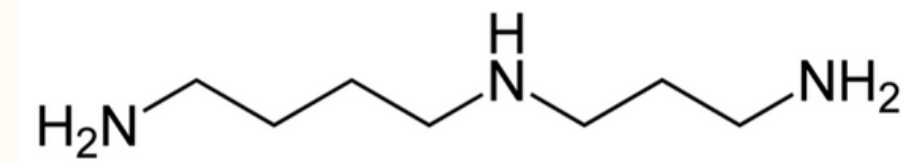
# Latest research on Spermidine &



# Spermidine

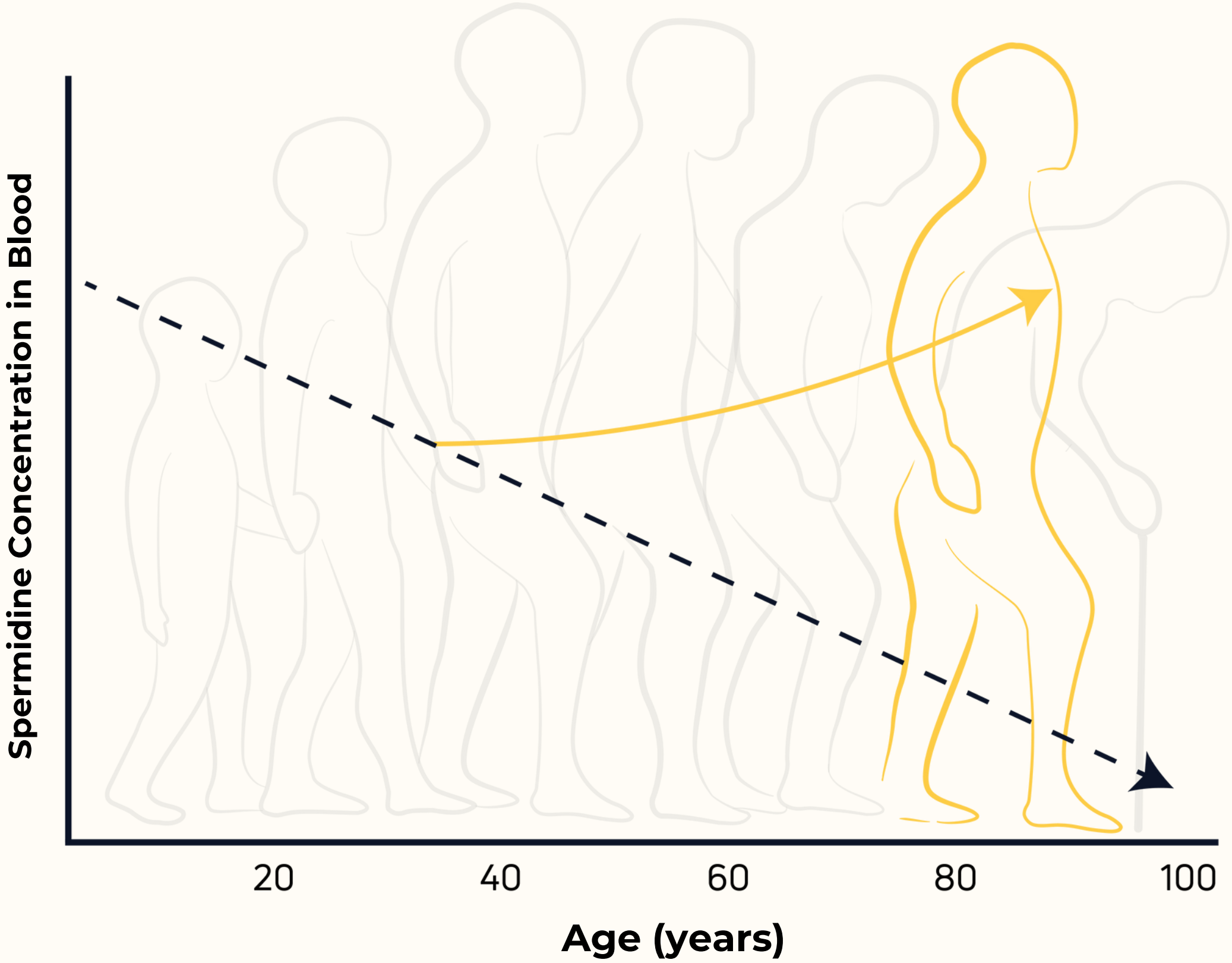
## A natural substance

- Natural polyamine
- Occurs in all cells (humans, animals, plants, fungi/yeasts)
- Important component of our diet
- Concentration decreases with age in humans



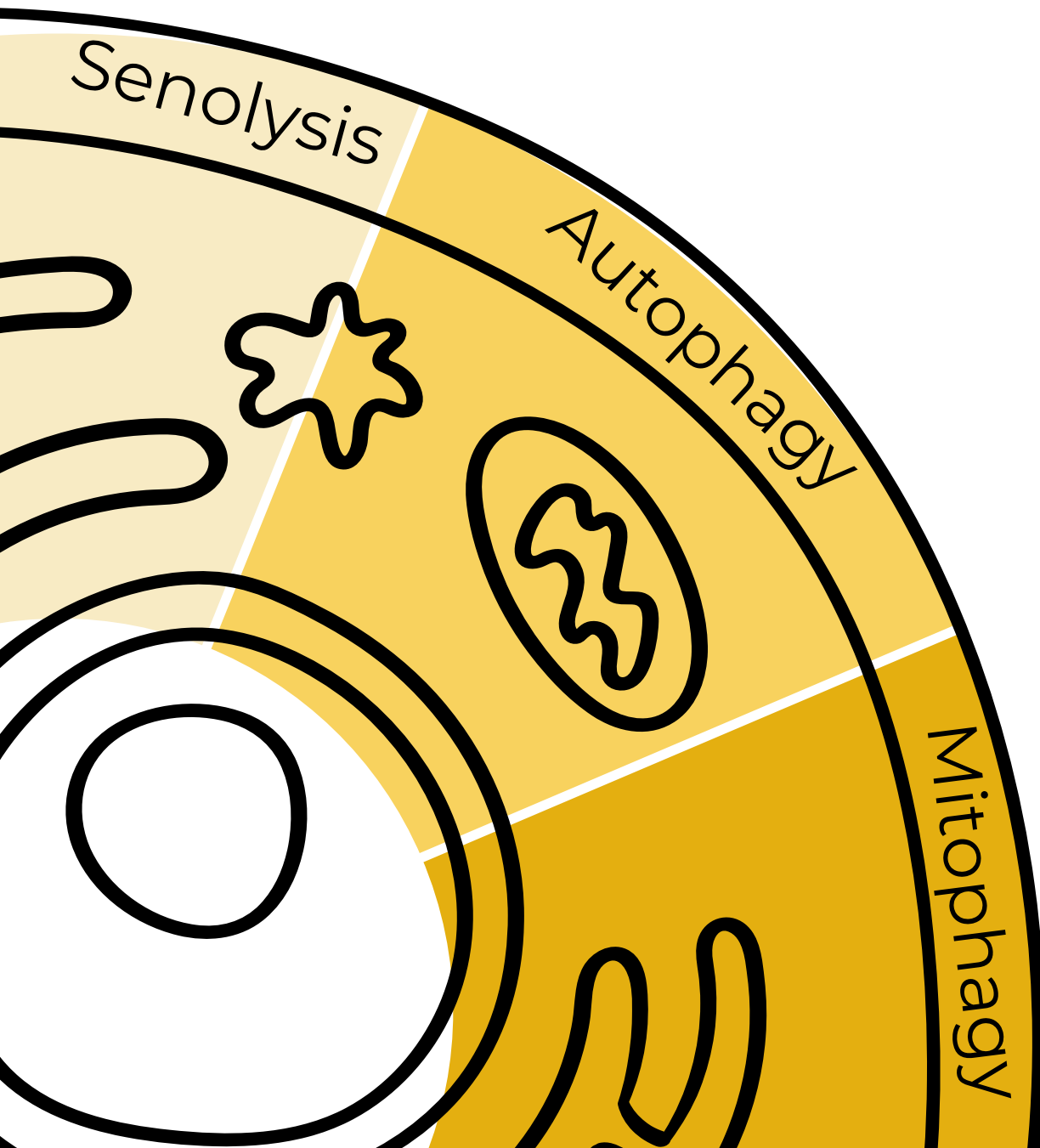
Spermidine sources of the human body

The spermidine concentration decreases with age...

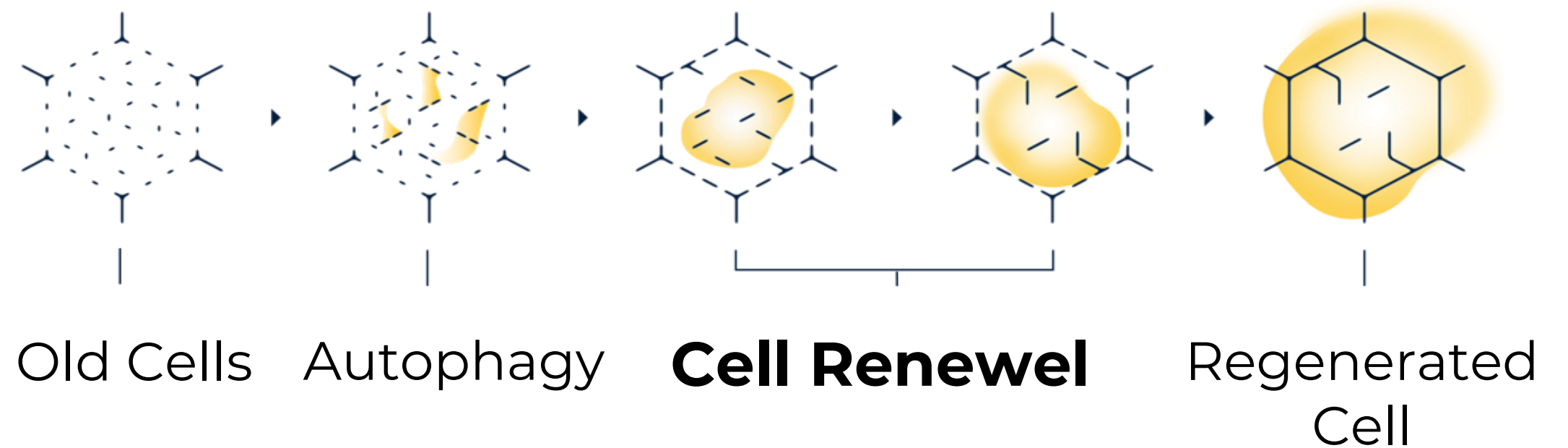


# The desire to live longer and healthier - longevity

Cleansing and cell renewal process through autophagy



## Spermidine activates autophagy

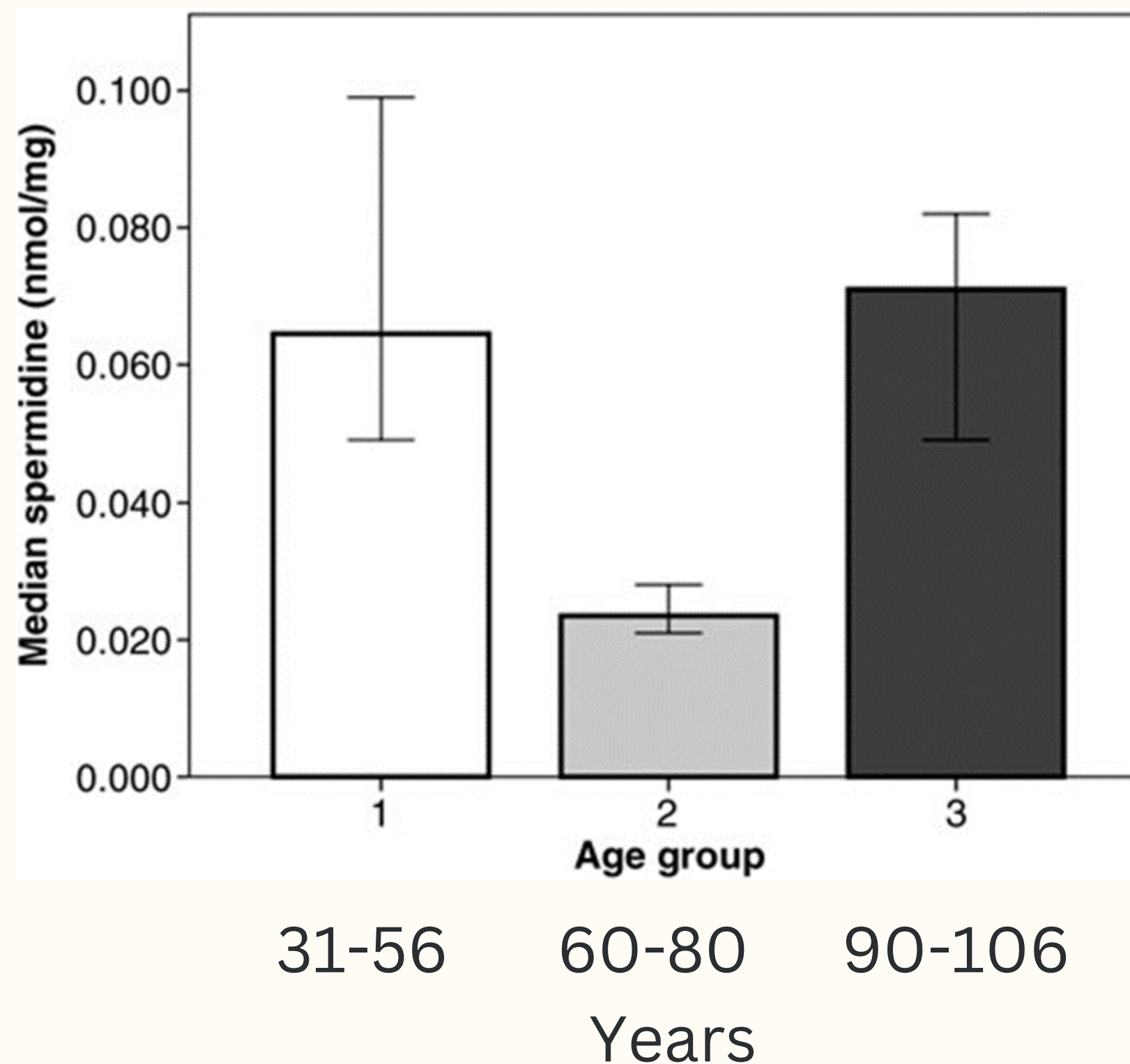


Autophagy - the process that keeps us young by removing cellular waste and converting it into energy

... but not in  
healthy people  
over 90 and 100  
years of age

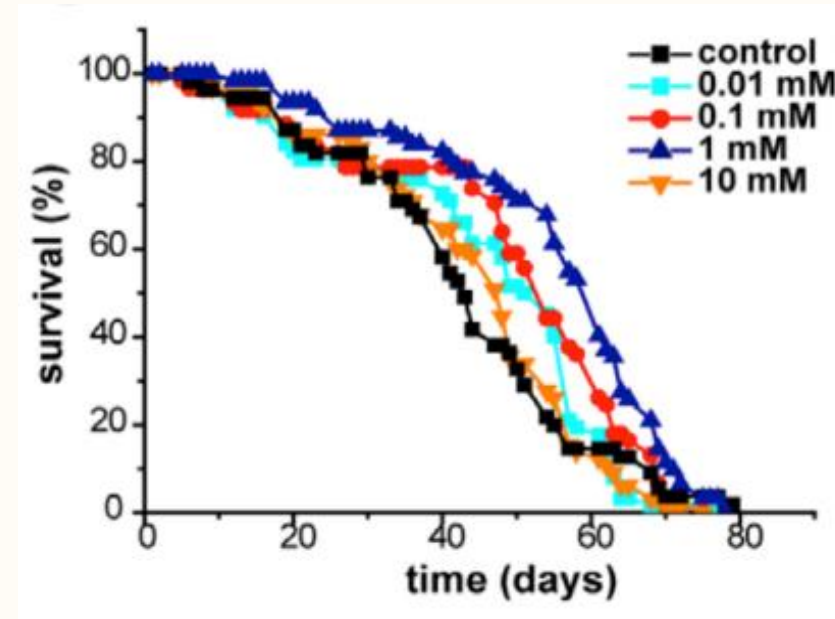
Spermidine was measured in the  
whole blood of healthy  
volunteers

Pucciarelli 2012, Rejuvenation Research

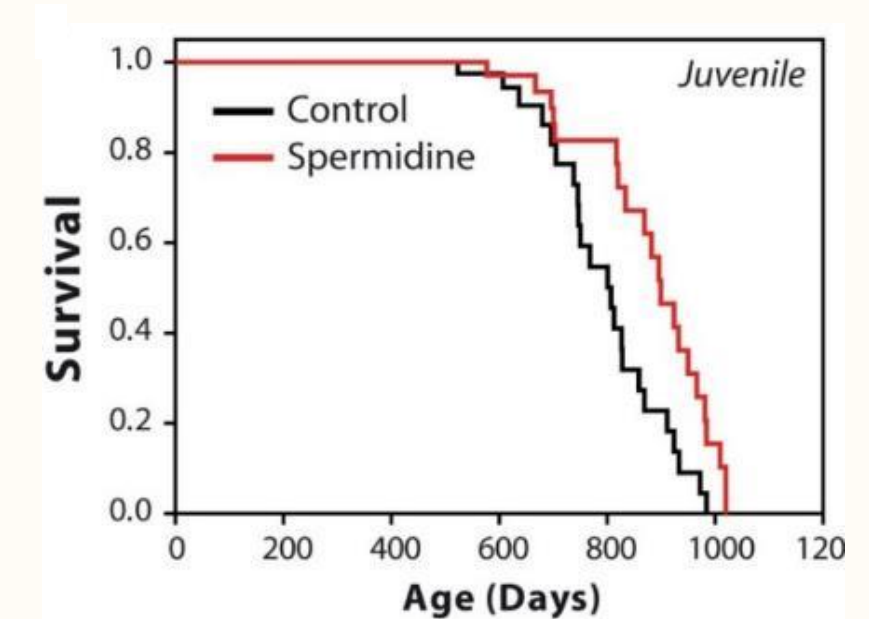


# Spermidine prolongs the life of various organisms

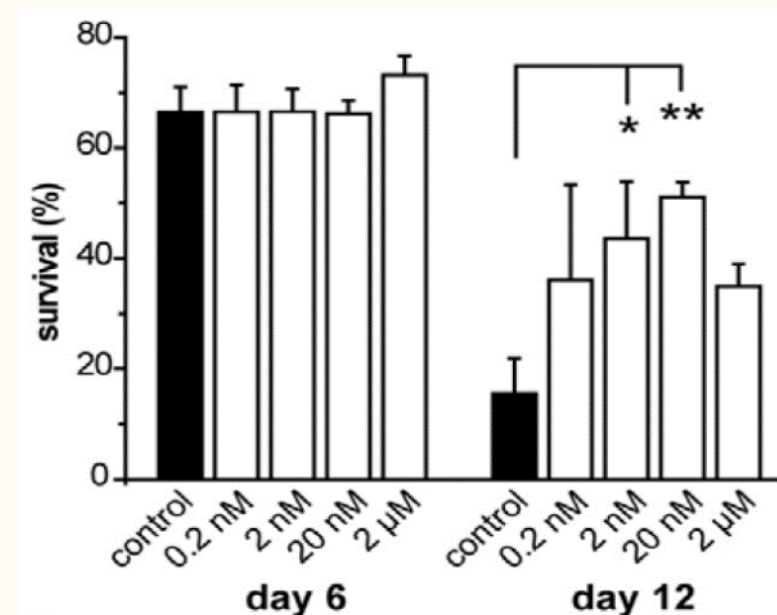
Eisenberg et al. 2009, Nature Cell Biology  
Eisenberg et al. 2016, Nature Medicine  
Ao et al. 2019, Sciences Advances



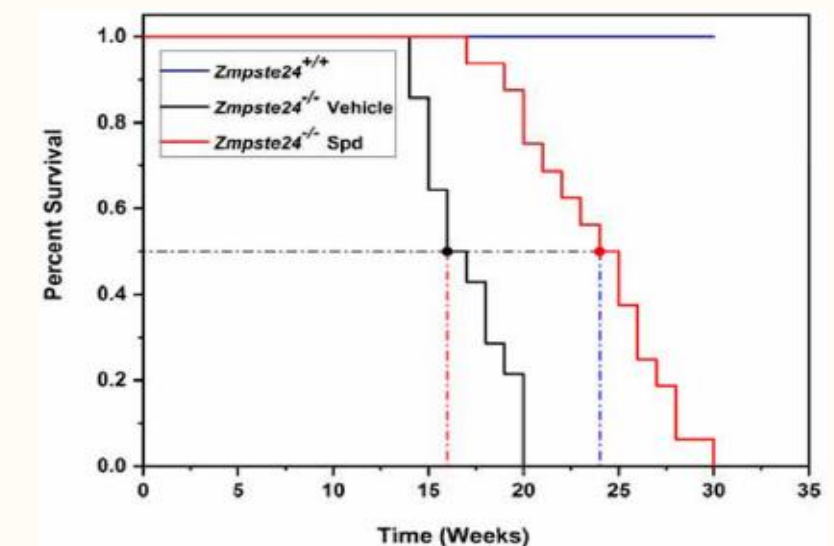
**Flies**



**Mice**



**Human (Cell Culture)**

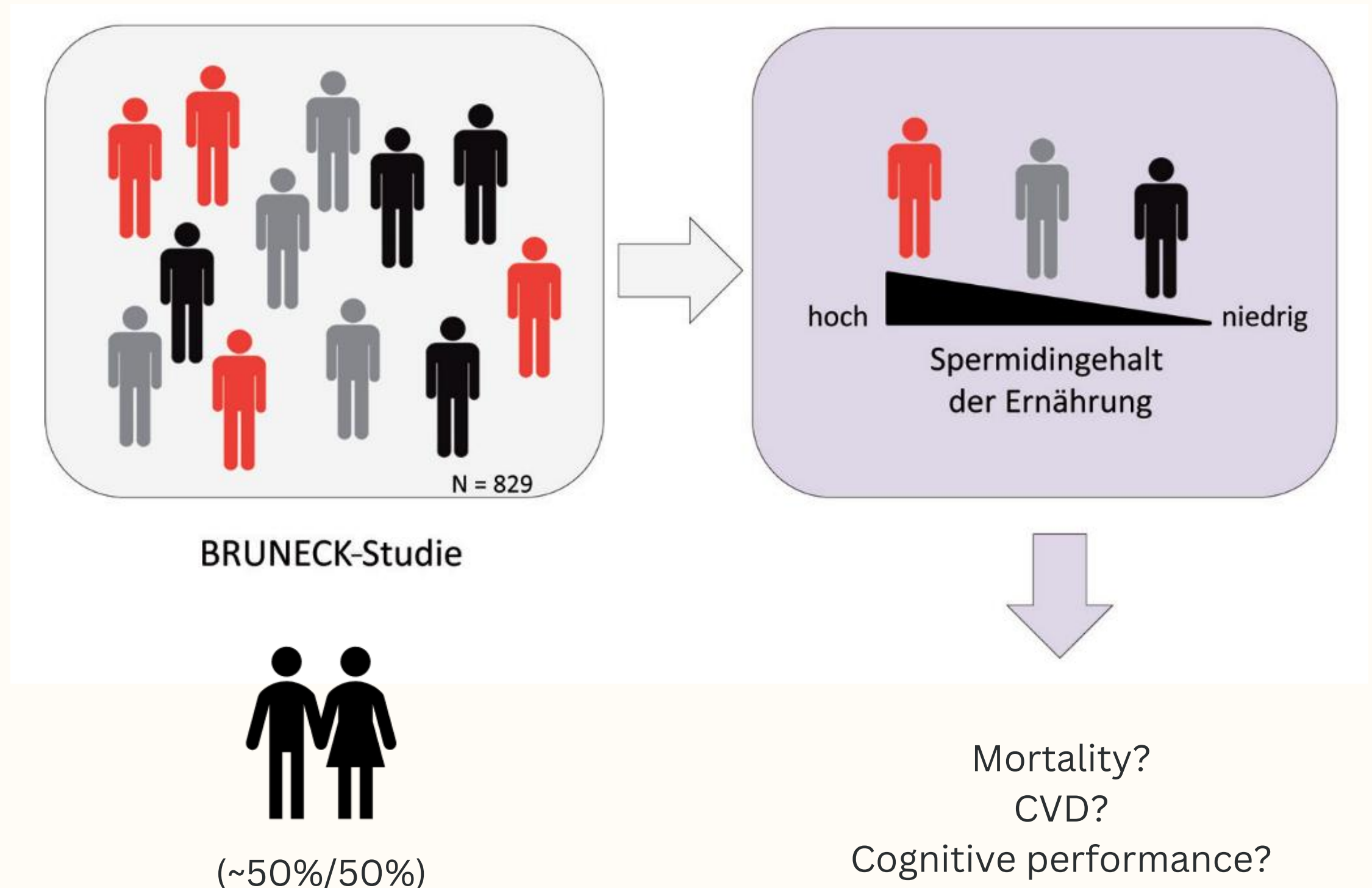


**Progeriatric Mice**

Does spermidine  
work in humans?

First indications  
come from  
epidemiology

Eisenberg & Sedej 2017, Nutrition News



# Higher spermidine intake – Lower mortality

**TABLE 2**  
Total mortality according to dietary polyamine intake<sup>1</sup>

	Tertile		
	Tertile 1 (low intake)	Tertile 2	Tertile 3 (high intake)
Spermidine group			
Person-years, <i>n</i>	4227	4353	4439
Deaths, <i>n</i>	171	103	67



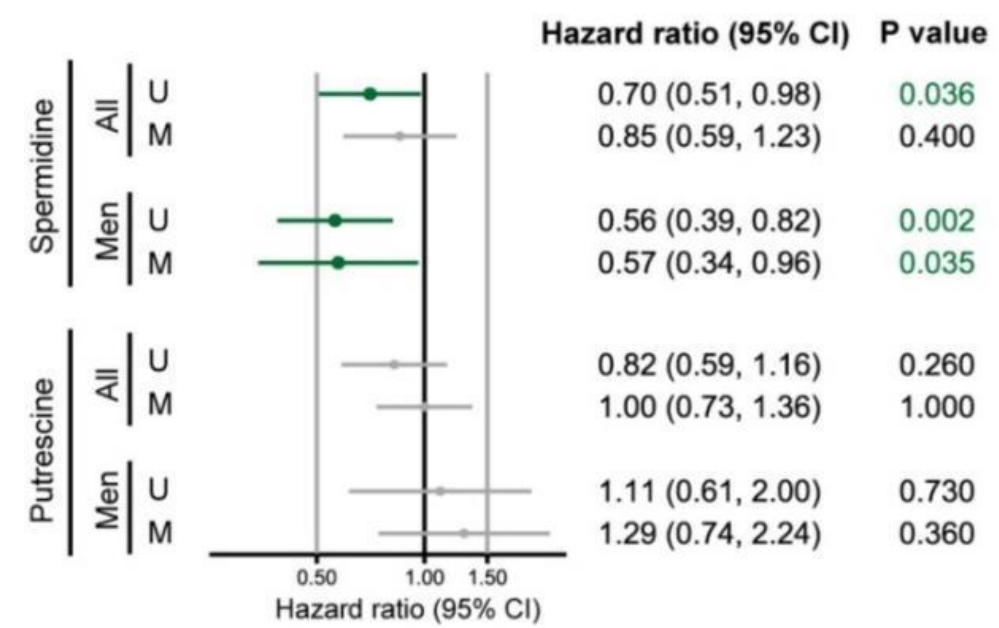
Average 5 years extended lifespan

People with more spermidine in their diet show a lower risk of cardiovascular diseases



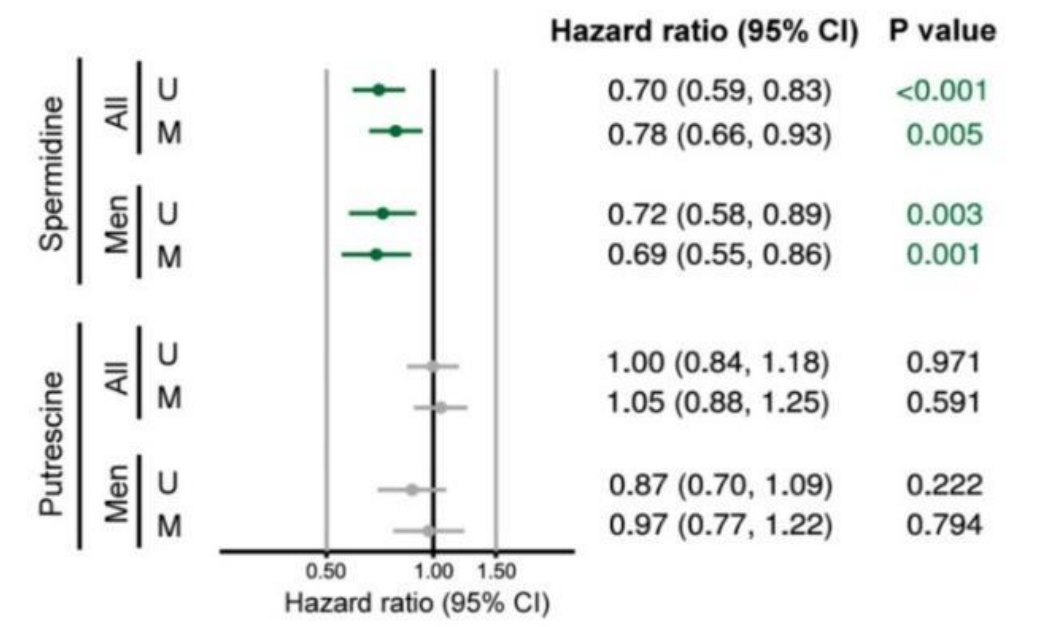
Reduced risk of deaths from heart failure

Death due to heart failure (1995–2010, n=25 of 791)\*



Reduced risk of occurrence of heart disease

Incident CVD (1995 – 2010, n=141 of 791)\*\*\*



# Spermidine is essential for fasting-mediated autophagy and longevity



Prof. Frank Madeo



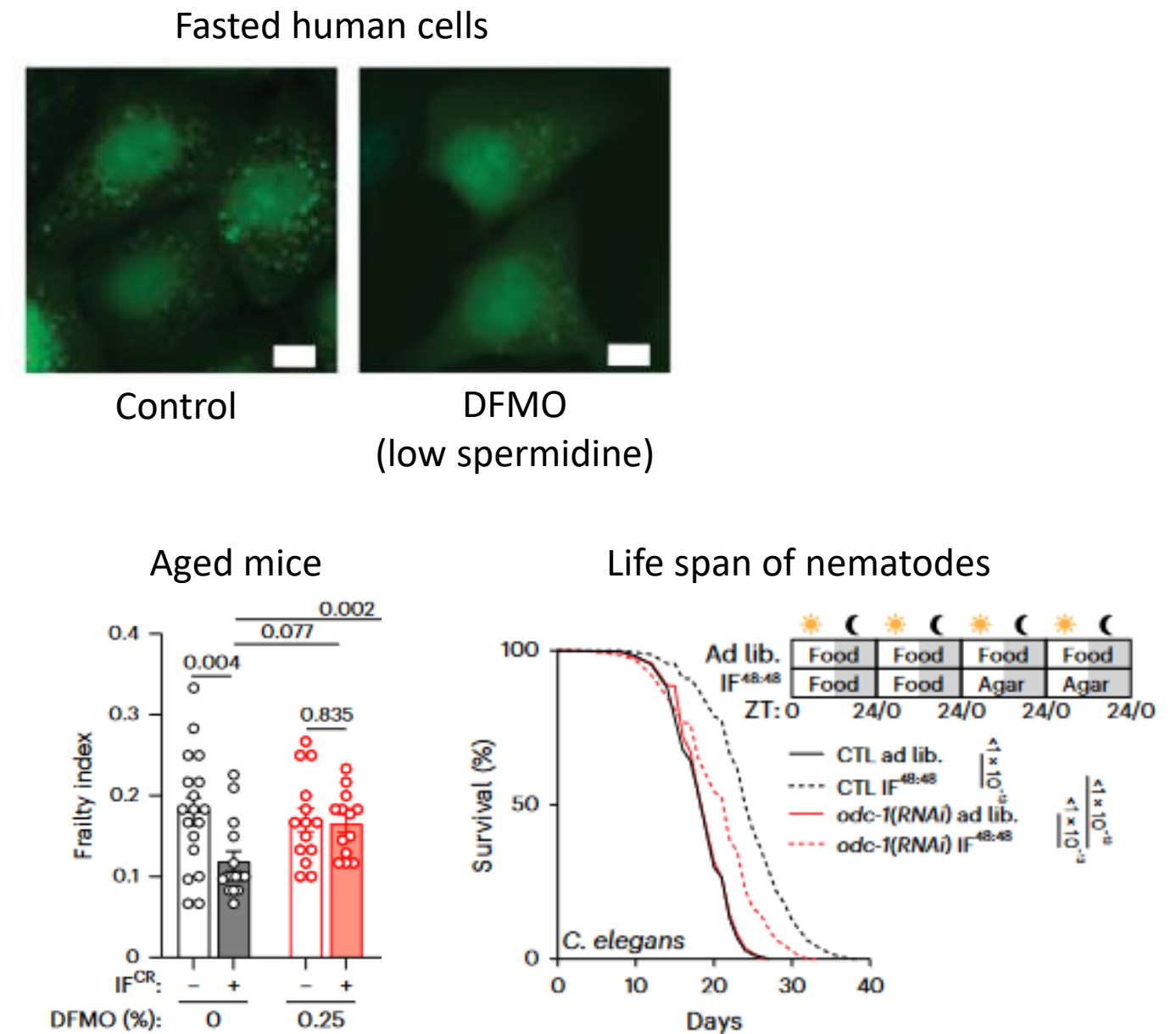
Prof. Tobias Eisenberg

Spermidine as Fasting Mimetic

Published  
2024

## Newest publication in Nature Cell Biology

In this study we demonstrate that spermidine is required for fasting-induced autophagy in human cells. Furthermore, blocking the spermidine in vivo in model organisms abrogates the lifespan- and healthspan-extending effects of fasting.



Hofer SJ, Daskalaki I, Bergmann M, Friščić J, Zimmermann A, Mueller MI, Abdellatif M, Nicastro R, Masser S, Durand S, Nartey A, Waltenstorfer M, Enzenhofer S, Faimann I, Gschiel V, Bajaj T, Niemyer C, Gkikas I, Pein L, Cerrato G, Pan H, Liang Y, Tadic J, Jerkovic A, Arahamian F, Robbins CE, Nirmalathasan N, Habisch H, Annerer E, Dethloff F, Stumpe M, Grundler F, Wilhelmi de Toledo F, Heinz DE, Koppold DA, Rajput Khokhar A, Michalsen A, Tripolt NJ, Sourij H, Pieber TR, de Cabo R, McCormick MA, Magnes C, Kepp O, Dengjel J, Sigrist SJ, Gassen NC, Sedej S, Madl T, De Virgilio C, Stelzl U, Hoffmann MH, Eisenberg T, Tavernarakis N, Kroemer G, Madeo F. Spermidine is essential for fasting-mediated autophagy and longevity. *Nat Cell Biol.* 2024 Aug 8. doi: 10.1038/s41556-024-01468-x. Epub ahead of print. PMID: 39117797.

# Current science on CelVio® Complex



## Study overview:

A review of the effects of autophagy and spermidine on age-related diseases.

The studies mentioned are only a small selection of scientific studies on spermidine. A larger selection can be found at the end of this presentation.

### Mental Health

- Protection against cognitive decline
- Prevention of dementia and Alzheimer's disease
- Reduction of inflammatory factors
- Reduction of stress and depression

### Immune system

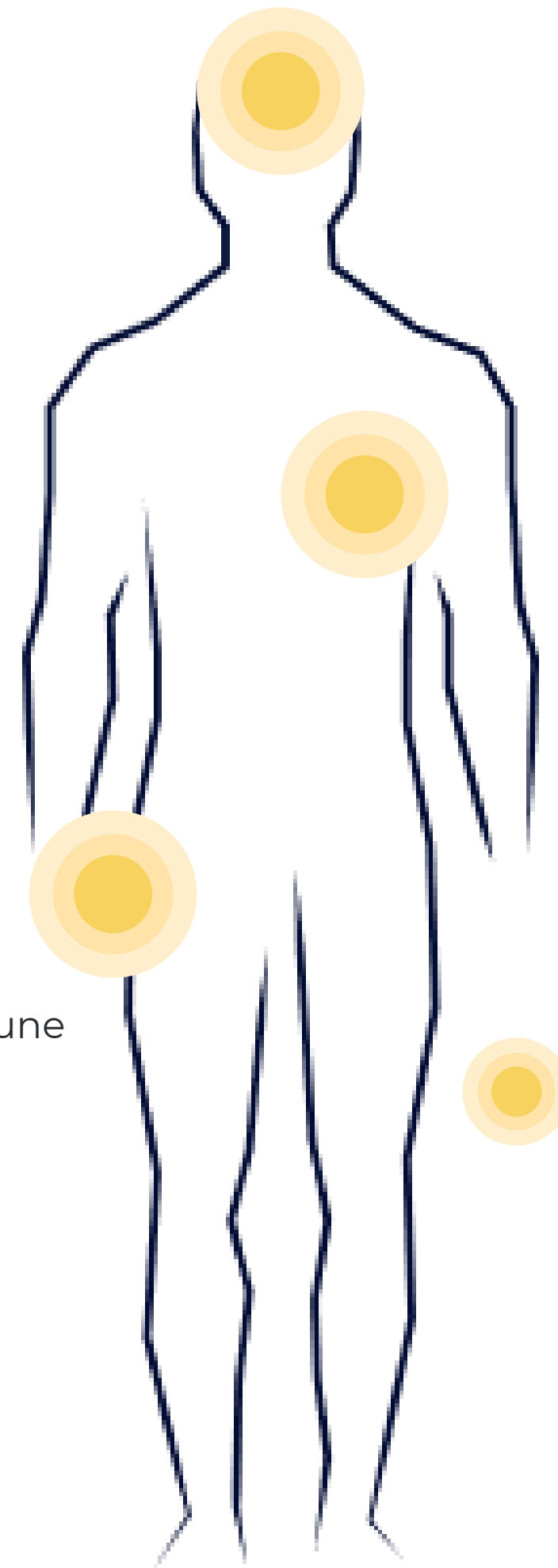
- Strengthening of the immune system
- Reduction of viral particles
- Adjuvant effects with vaccination

### Cardiovascular system

- Reduction of high blood pressure
- Strengthening the heart muscle
- Prevention of heart failure
- Increase of cellular respiration

### Aging and Longevity

- Reduction of age-related diseases
- Prolongation of healthy life span
- Synergistic effects with fasting



# Spermidine promotes the regeneration of cells after severe stress

The studies mentioned are only a small selection of scientific studies on spermidine. A larger selection can be found at the end of this presentation.

## **Study on muscle regeneration:**

A study by Eisenberg et al (2009) shows that spermidine stimulates autophagy and thereby promotes the regeneration of muscle cells after injury. This could be beneficial for athletes, as muscle regeneration is important after intensive training sessions.

## **Improvement of cardiovascular health:**

A study by Madeo et al (2018) suggests that spermidine may improve cardiovascular health, which could indirectly support athletic performance and recovery. A healthy cardiovascular system is crucial for recovery after exercise.

## **Reduction of inflammation:**

Research, such as that by LaRocca et al (2013), suggests that spermidine has anti-inflammatory properties. Inflammation is a natural part of the recovery process after exercise, but excessive inflammation can delay recovery. Spermidine may help regulate this inflammation.

## **Cellular health and longevity:**

A review paper by Eisenberg et al (2016) describes that spermidine can extend the lifespan of cells and promote their health. In the long term, this could also improve the body's ability to regenerate after exercise.

To prove the efficacy of **Celvio® Complex** we are also conducting our own clinical studies

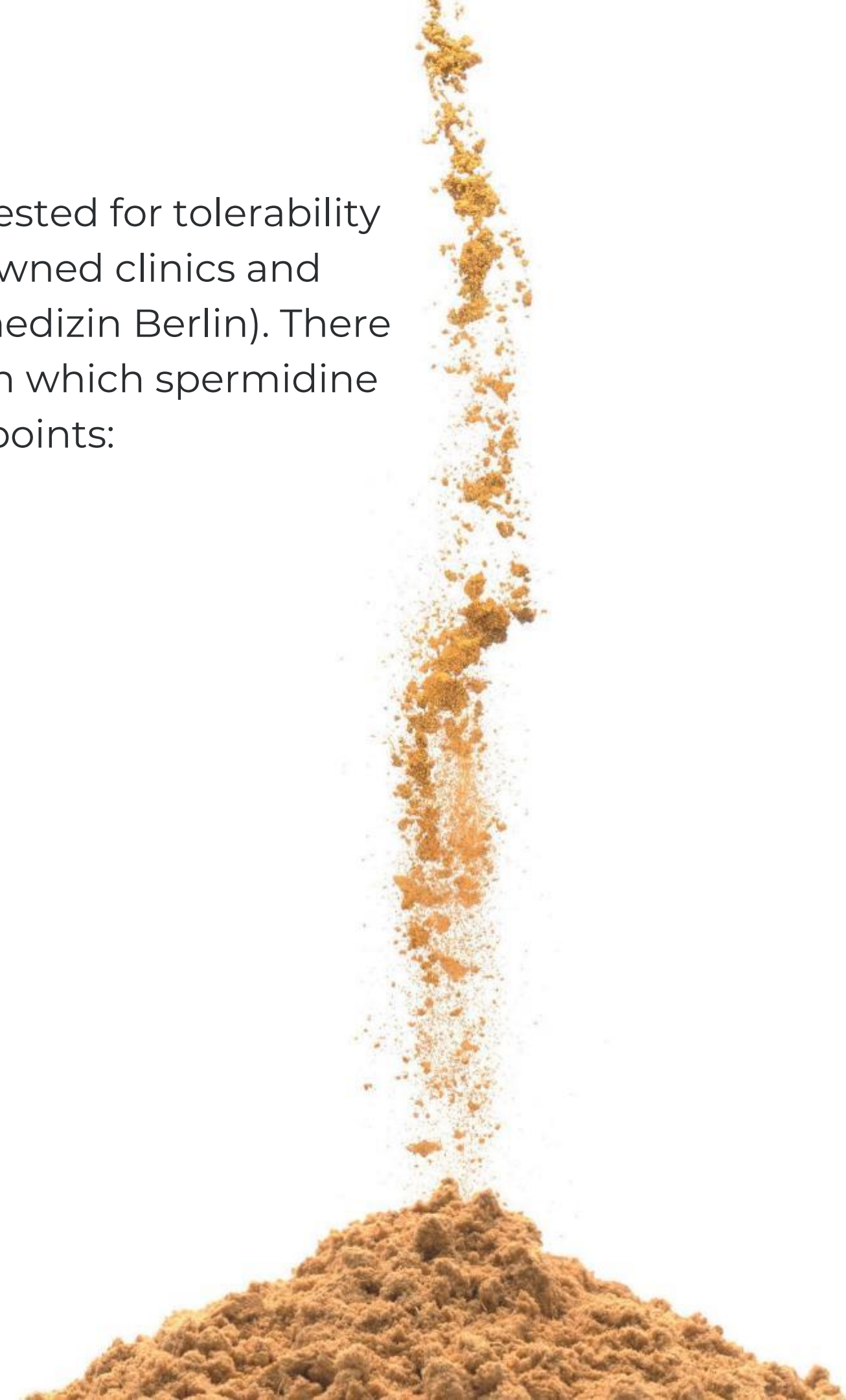
### **Celvio® Complex**

is based on the research results of the Karl-Franzens-University Graz.

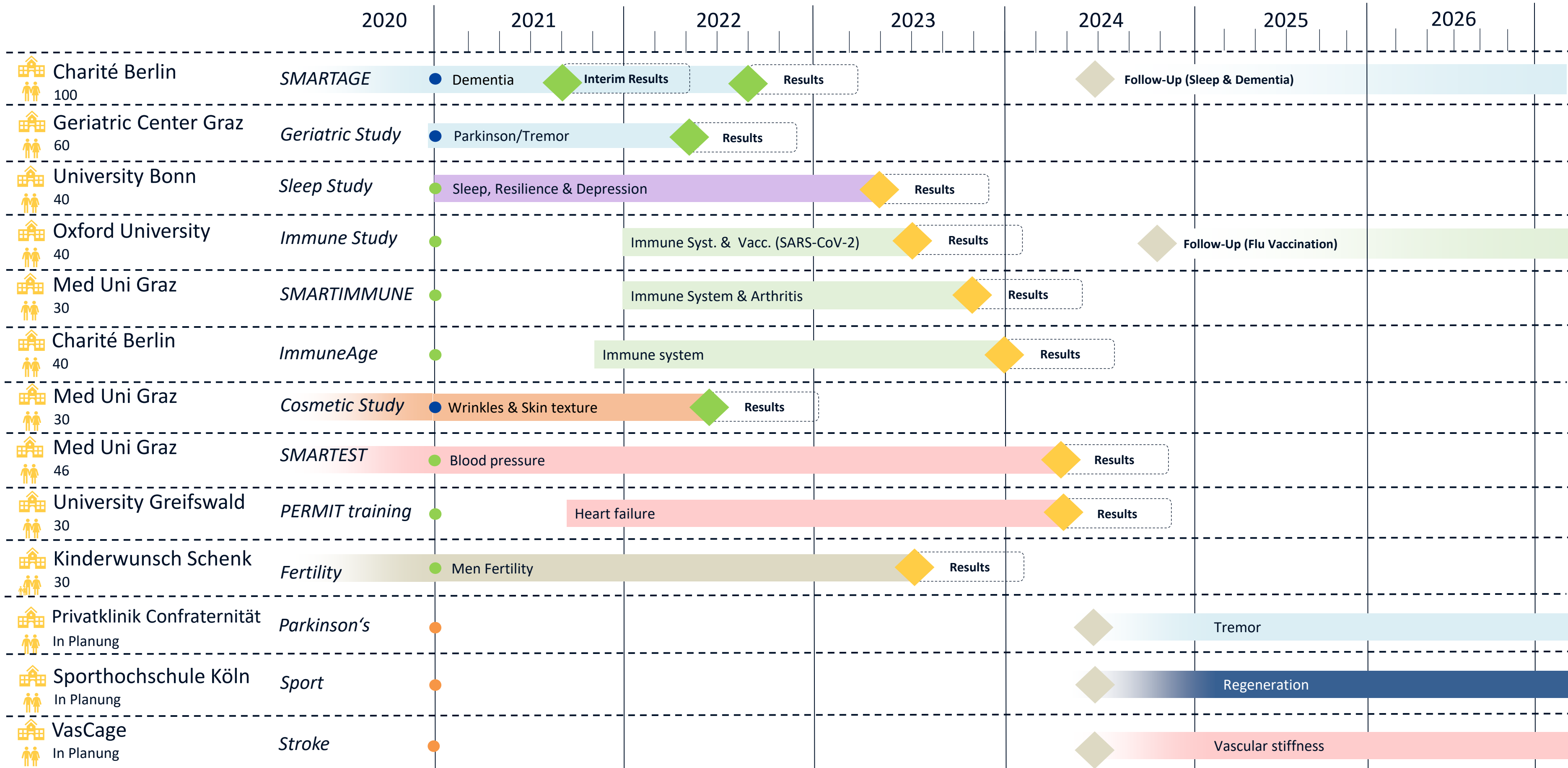
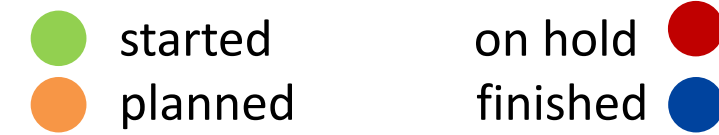
Through several years of collaboration, we have created the world's first natural wheat germ extract to activate autophagy.

**Celvio® Complex** has been clinically tested for tolerability and efficacy by independent and renowned clinics and universities (e.g. Charité, Universitätsmedizin Berlin). There are a large number of animal studies in which spermidine was used as a drug with different endpoints:

- Neurodegeneration
- Protection of the cardiovascular system
- Ageing and longevity
- Metabolism
- Fertility
- Muscle
- Reduction of cellular stress
- Immune system
- Skin and hair



# Study Status 2024



# Extract based on clinical studies



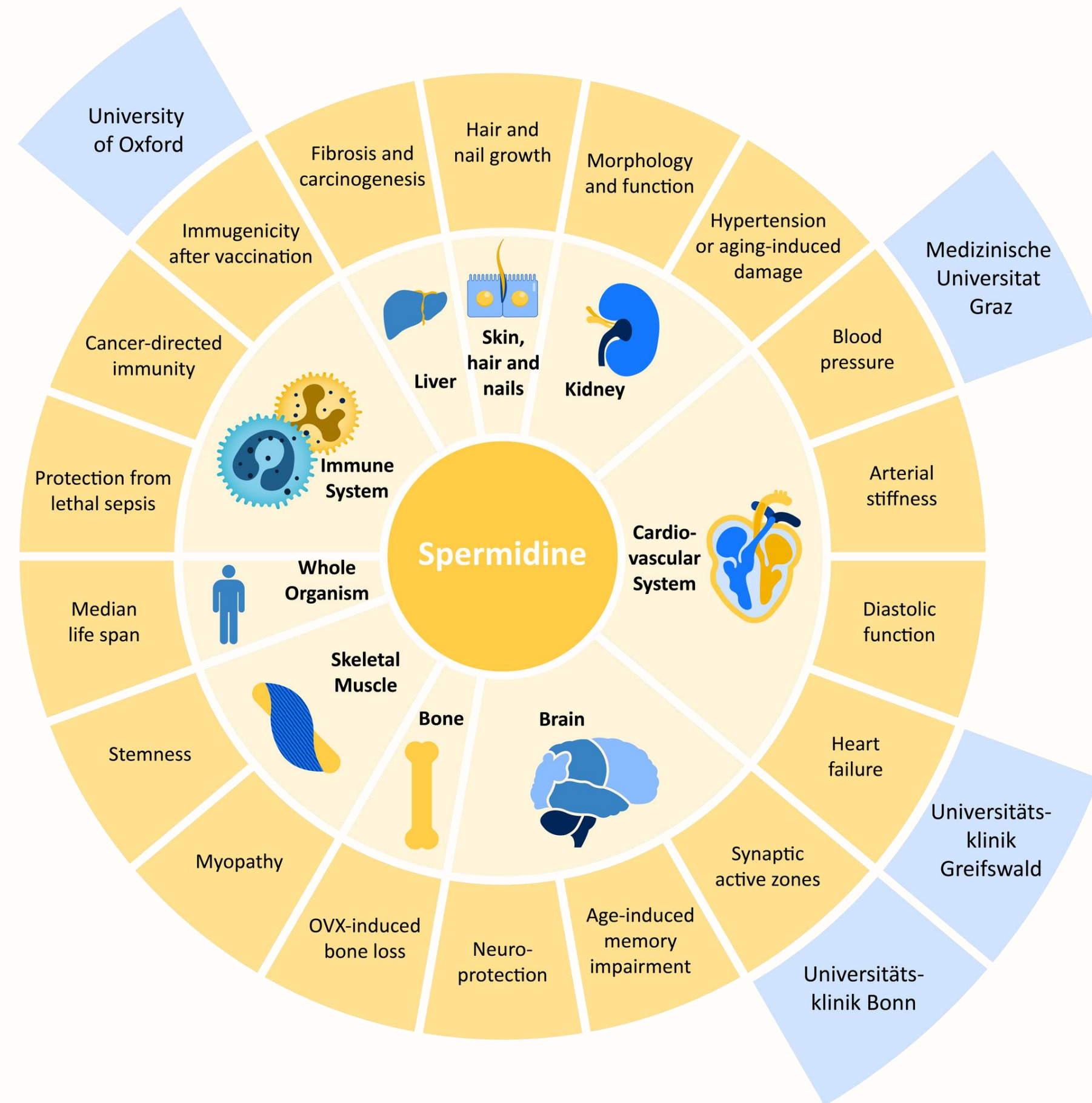
# Published studies on **CelVio® Complex**

- Toxicological study and safety of the product **CelVio® Complex**:  
<https://pubmed.ncbi.nlm.nih.gov/29315079/>
- SmartAge - Studie investigates the positive effects of spermidine on memory performance of elderly people. In cooperation with the Charité Berlin.  
protocol: <https://pubmed.ncbi.nlm.nih.gov/31039826/>  
first results: <https://pubmed.ncbi.nlm.nih.gov/30388439/>
- Hippocampal volume and overall "brain health".  
based on cohorts from the SmartAge study:  
<https://pubmed.ncbi.nlm.nih.gov/32629145/>
- Nursing patient study at the Geriatric Health Centers in Graz focusing on Parkinson's disease and tremor:  
[https://ggz.graz.at/de/content/download/4924/64919/version/3/file/GGZ\\_Magazin\\_2022\\_web.pdf](https://ggz.graz.at/de/content/download/4924/64919/version/3/file/GGZ_Magazin_2022_web.pdf)



# Current ongoing clinical studies with **CelVio® Complex**

- Improving Vaccination in Older Adults by Inducing Autophagy With Spermidine  
<https://clinicaltrials.gov/ct2/show/NCT05421546term=spermidine&draw=2&rank=1>
- Spermidine Anti-Hypertension Study (SMARTTEST)  
<https://clinicaltrials.gov/ct2/show/NCT04405388term=spermidine&draw=2&rank=3>
- An Exploratory Clinical Study on Autophagy and Multi-level Molecular Profiling During Spermidine Supplementation  
<https://clinicaltrials.gov/ct2/show/NCT04823806?term=spermidine&draw=2&rank=2>
- Spermidine supplementation on Metabolic, Neuronal and Cardiovascular Response to Exercise TRAINING (PERMIT\_EX)  
<https://clinicaltrials.gov/ct2/show/NCT05128331?term=spermidine&draw=2&rank=6>



# Upcoming studies on CelVio<sup>®</sup> Complex



# A game-changing study: TLL's "Sleep and Anti-Depression Study"

Target: To evaluate the influence of novel food wheat germ extract with high spermidine content on autophagic activity in people with affective, psychotic, and/or dependency disorders.

**Clinic:** Clinic for Psychiatry and Psychotherapy, Uniklinikum Bonn

**Director of studies (Lab):** Dr. Nils C. Gassen

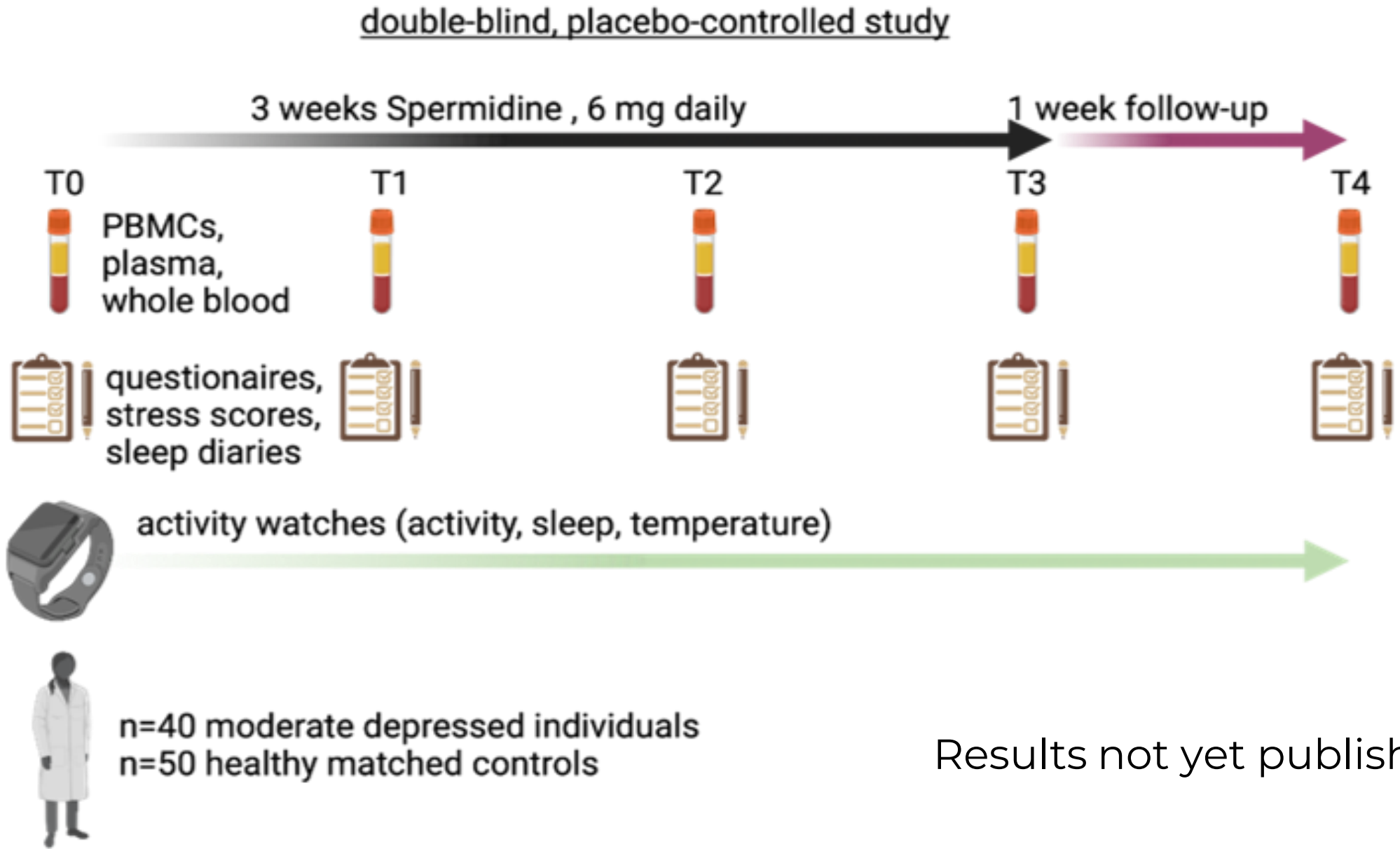
**Link to pre-publication:** <https://pubmed.ncbi.nlm.nih.gov/39677641/>

**Study Management (Clinic):** Dr. Christine Niemeyer

**Synopsis:** The study investigates the influence of high spermidine wheat germ extract on stress signaling pathways, autophagy activity, sleep behavior and well-being in depressed patients and healthy controls. An extensive multi-omic analysis will also be performed. The goal is to find a new therapeutic option for psychiatric patients with few side effects.

# A game-changing study: TLL's "Sleep and Anti-Depression Study"

A double-blind, randomized, placebo-controlled clinical trial with healthy & depressed subjects aged between 20- and 70-years intake of wheat germ extract with a high spermidine content of 4 mg for 3 weeks. Dexamethasone suppression test to investigate of stress resilience takes place immediately after the end of the 21-day intake period. The measurements of sleep quality are carried out using questionnaires and the wearing of altigraphs.



Results not yet published

# A game-changing study: TLL's "Sleep and Anti-Depression Study"

Polyamine metabolism plays an important role in the pathophysiology of depression. Spermidine could be a promising new treatment option for depressive patients.

## Key Findings

### Polyamine Metabolism

Polyamines are natural compounds that play a role in many biological processes. An imbalance in polyamine metabolism has been found in both depressed patients and animal models.

### Mechanisms

Stress leads to the downregulation of an important enzyme (LACCI), resulting in increased ratios of ornithine to putrescine. This change has been observed in both humans and mice, suggesting it could be a potential biomarker for depression.

### Spermidine Treatment

In a clinical study with depressed patients, a three-week treatment with spermidine, a natural polyamine, was found to reduce depression symptoms. These results were confirmed by experiments on mice exposed to chronic social defeat stress.

### Acute Stress

In an experiment with healthy participants who performed a bungee jump, acute stress was also found to affect polyamine metabolism. This was evidenced by altered ornithine-to-putrescine ratios compared to non-stressed individuals.

# Spermidine improves vaccine responses and autophagy in healthy older adults

Target: The study investigates the influence of spermidine on the immune response and vaccination efficiency of older adults after SARS-CoV-2 vaccination.

**Clinic:** Oxford University, England

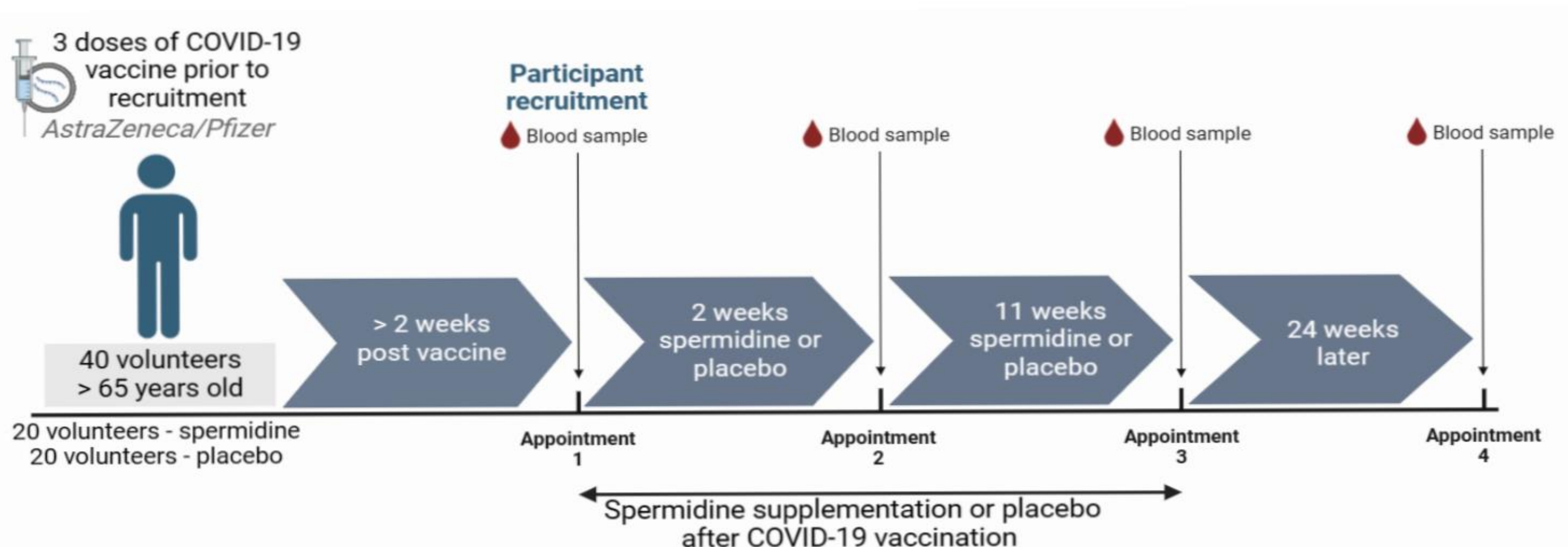
**Director of studies (Lab):** Prof. Katja Simon

**Study Management (Clinic):** Dr. Lucy Jones

**Synopsis:** Older adults are at higher risk for infectious diseases, and vaccines are less effective in this age group compared to younger people. This reduced efficacy is partly due to a decline in autophagy, a process that is critical for maintaining memory T and B cell responses necessary for successful vaccination. Spermidine, a naturally occurring polyamine, has been shown to induce autophagy in various cell types and improve immune responses in aged mice and human immune cells in culture. However, its effects on human immunity were previously unexplored.

# Spermidine improves vaccine responses and autophagy in healthy older adults

A double-blind, randomized, placebo-controlled clinical trial was conducted with 40 volunteers over the age of 65. Participants received either 6 mg spermidine per day or a placebo after the third dose of a COVID-19 vaccine. The aim of the study was to evaluate changes in neutralizing antibody titers against SARS-CoV-2 and other markers of immune responses important for vaccine efficacy over 3 months of spermidine treatment.



# Spermidine improves vaccine responses and autophagy in healthy older adults

The results suggest that spermidine can improve vaccination responses in older adults, particularly those with initially weak or even absent immune responses. This study is the first to show improved autophagic flux in immune cells of older adults after spermidine treatment, indicating its potential as an affordable postvaccinal intervention with immune-boosting effects.

## Key Findings

1. Neutralizing antibodies: spermidine increases antibody titers against SARS-CoV-2.
2. Immune non-responders: Improved immune responses and vaccination efficacy in participants with low initial antibody titers. In these subjects (immune non-responders, i.e. people who showed a poor or no vaccination response at the start of the study) were also found:
3. Autophagy and cell function: Spermidine promotes autophagy and improves immune cell functions.
4. Transcriptional signature: unique signature in memory B cells important for the vaccination effect by spermidine.
5. Cellular senescence: spermidine reduces cell senescence.

Starts in  
2024

# Autophagy-Enhancers to reduce sleep disturbances: a combined approach

Target: To determine the impact of spermidine on sleep physiology and sleep-dependent memory consolidation, and help shed light on the mechanisms underlying this association

**Clinic:** Agnes Flöel, Greifswald, Stephan Sigrist, Charité Berlin

**Director of studies (Lab):** Prof. Agnes Flöel, Charité Berlin

**Study Management (Clinic):** Dr. Silke M. Wortha, Greifswald

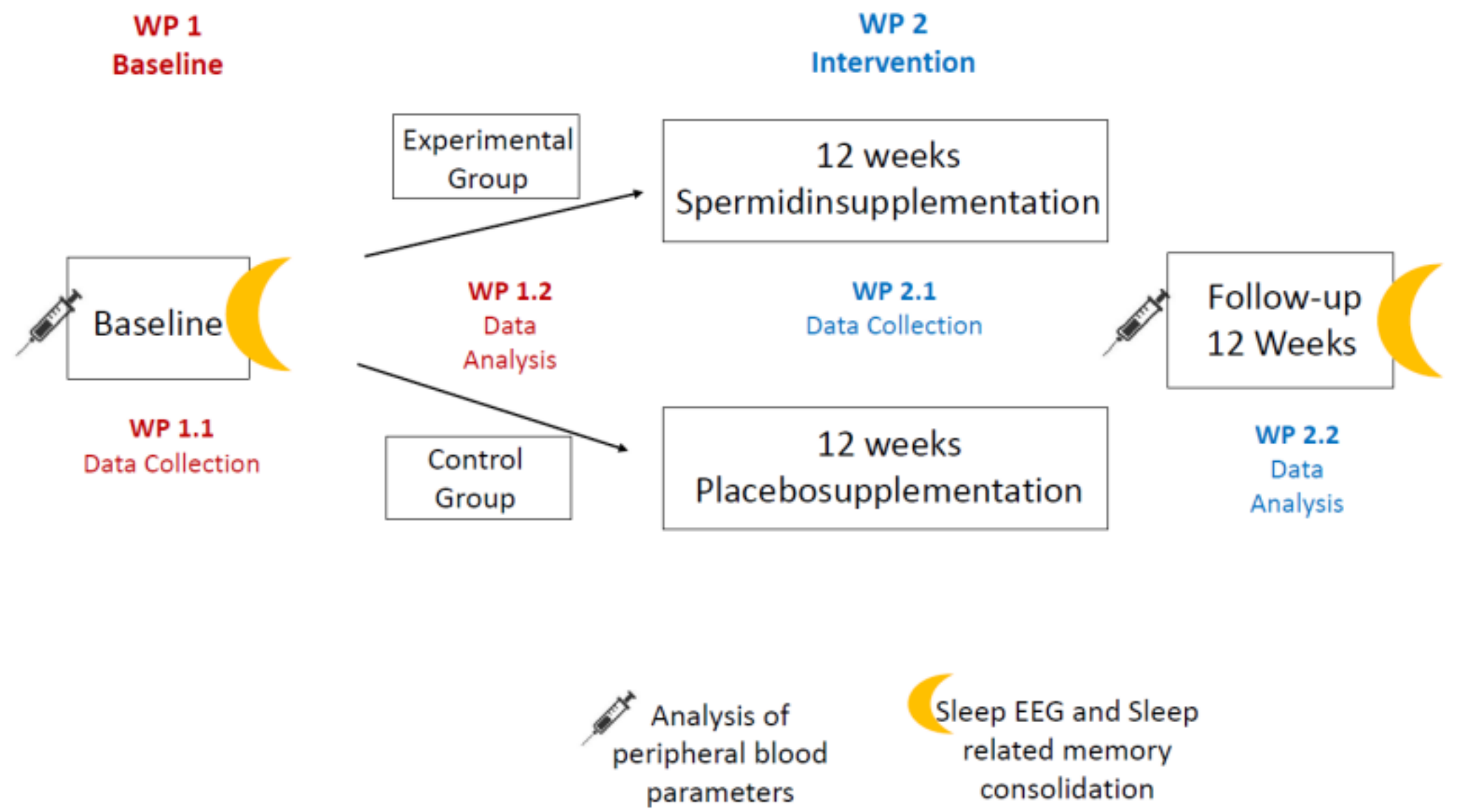
**Synopsis:** Effects of Spd-S on sleep parameters (coupling between SO and spindles (primary); as well as SO and spindle power) compared to placebo group.

Secondary endpoints: Effects of Spd-S on sleep related memory consolidation (i.e., visuospatial memory task, verbal memory task, and procedural task) after sleep compared to placebo control group. Differences in insulin-glucose metabolism, neuropeptides, markers of autophagy, between spermidine and placebo group.

Starts in 2024

# Autophagy-Enhancers to reduce sleep disturbances: a combined approach

Target: To determine the impact of spermidine on sleep physiology and sleep-dependent memory consolidation, and help shed light on the mechanisms underlying this association



Starts in  
2024

# IRFLUVA- 'Improving the Long-Term Immune Response to Flu Vaccine'

Target: The study investigates the influence of spermidine on the immune response and vaccination efficiency of older adults after flu vaccination.

**Clinic:** Cardiff University, England

**Director of studies (Lab):** Prof. Katja Simon

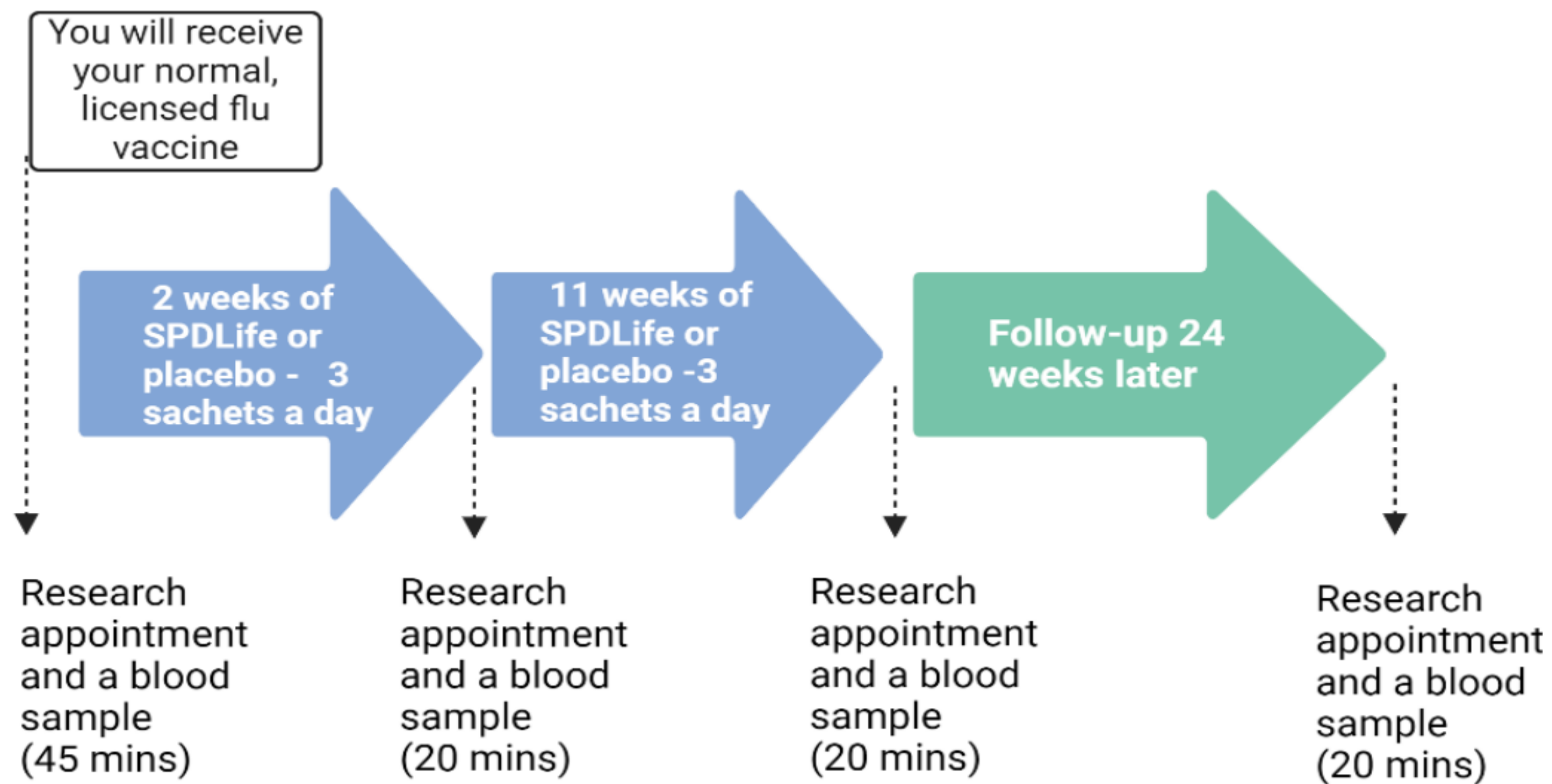
**Study Management (Clinic):** Dr. Lucy Jones

**Synopsis:** The principal objective of this study is to determine the feasibility of recruitment and retention of participants to the study, tolerability of daily SpermidineLife (SPDLife) dietary supplements following vaccination for flu, acceptability of the protocol, and side-effects to SpermidineLife supplements. We will use the data we collect to perform a power calculation for future later phase studies and improve study design.

Starts in 2024

# IRFLUVA- 'Improving the Long-Term Immune Response to Flu Vaccine'

Target: The study investigates the influence of spermidine on the immune response and vaccination efficiency of older adults after flu vaccination.



# Publicly available studies on spermidine



# Spermidine could be supportive/preventive for the following indications/diseases:

Category	Indication/disease	Source
<b>Neurodegeneration</b>	Parkinson, Dementia, Alzheimer	1,2,3,4,5,6,7,8, 55,56,57
<b>Immune system</b>	Immunization failure in immune senescence, SARS-CoV-2/COVID-19 (risk groups), regenerative capacity of epithelia in lung tissue.	9,10,11,12,13,14,15,16,17,18,54,62
<b>Ageing &amp; Longevity</b>	Life extension, senescence delay of cells, better mitochondrial function.	19,20,21,22,23,24,25,26
<b>Liver</b>	Hepatic fibrosis, hepatocellular carcinoma, liver damage by alcohol, liver protection by NRF2 signaling, nonalcoholic steatohepatitis.	27,28,52,53,58
<b>Digestion</b>	Inflammation in the intestine	27,28,52,53,58
<b>Skin &amp; Hair</b>	Neurodermatitis, creatine production, hair loss, restoration of skin barrier function, accelerated wound healing, hypopigmentation, increase melanin production.	29,30,59
<b>Heart</b>	Atherosclerosis, Aortic Aneurysm, Cardiovascular Disease, Peripheral Arterial Disease, Systemic Inflammation	31,32,33,34,35,36,37,38,60
<b>Bones &amp; Cartilage</b>	Bone density, intervertebral disc degeneration (IDD), SPD increases cartilage mass.	39,40,41,42,43,61
<b>Muscles</b>	Age-related muscular atrophy	44,45
<b>Diabetes &amp; Obesity</b>	Metabolic disturbance in overeating, glucose tolerance, regulation of lipid metabolism, reduction white adipose tissue, decreased inflammatory cytokines and chemokines.	46,47,48,49,50,51,65

# Overview of the most recent studies on spermidine



## 1. Neurodegeneration<sup>1,2,3,4,5,6,7,8, 55,56,57</sup>

By activating autophagy, toxic protein aggregates in cells can be removed, which are responsible for diseases such as Parkinson's, dementia, Alzheimer's or ALS. This has been demonstrated both in mice and by human studies. The degradation of neurons and associated disease patterns can be curbed. Spermidine activates the autophagic process and can be both preventive and protective. Spermidine protects the brain from premature aging and mitochondrial dysfunction. Higher spermidine intake is also associated with greater hippocampal volume. Spermidine can cross the blood-brain barrier, where it improves mitochondrial function. This reduces the risk of cognitive impairment. A low concentration of spermidine protected against neuronal toxicity caused by paraquat, while both low and high concentrations provided protection against cytotoxicity caused by overexpression of amyloid precursor protein.



## 2. Immune system<sup>9,10,11,12,13,14,15,16,17,18,54, 62</sup>

Spermidine supplementation reduces inflammatory cytokines and leads to increased memory cell formation. It also promotes the differentiation of T immune cells, resulting in better vaccination success in the elderly. Autophagy plays an important role in immune defense and on the one hand can help to dispose of pathogenic microorganisms. On the other hand, autophagy still fulfills an important function in mediating immunological memory and improves it in old age. Autophagy induced by spermidine can reduce the viral load of SARS-CoV-2 infected cells by 85%. Spermidine leads to a protective effect against inflammatory bowel diseases such as acute colitis. The polyamine metabolism of pneumococci has far-reaching effects on its capsular stability, thus influencing the pathogenicity of the virus. Spermidine treatment induces autophagy and increases the regenerative capacity of epithelia harvested from mouse lung tissue. Spermidine could thus reduce allergic/asthmatic lung reactions. Spermidine & Eugenol is an innovative combination therapy capable of stimulating autophagy and reducing inflammation in vitro. This may be promising for COVID-19 risk groups.

# Overview of the most recent studies on spermidine



## 3. Aging and Longevity<sup>19,20,21, 22,23, 24, 25, 26</sup>

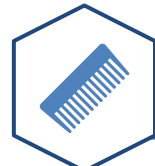
Spermidine and autophagy levels decrease with older age in the human body. Spermidine supplementation can replenish the spermidine pool, induces autophagy in the body and leads to life extension in mice. In addition, a long-term epidemiological study (20 years) demonstrated that higher consumption of spermidine-containing foods correlated with reduced mortality and 5 years longer life expectancy. Oral administration of spermidine greatly increases mitochondrial function in high-fat diet mice and reduces inflammatory markers. Spermidine can delay cell senescence and senescence-induced inflammatory processes. The life-prolonging effect of spermidine is thought to be due in part to its protection of nuclear DNA.



## 4. Digestion and liver<sup>27,28,52,53,58</sup>

Liver damage caused by excessive alcohol consumption could be reduced or even reversed by spermidine. Spermidine acts as an antioxidant and can thus break down harmful reactive substances. Spermidine also appears to prevent intestinal inflammation, which also suggests that it has an antioxidant effect. Spermidine mediates liver protection by enhancing NRF2 signaling via a MAP1S-mediated non-canonical mechanism. Spermidine prolongs lifespan and prevents both liver fibrosis and hepatocellular carcinoma by activating MAP1S-mediated autophagy. Spermidine treatment partially restores protein synthesis and mitochondrial function in non-alcoholic steatohepatitis (NASH) and prevents NASH progression in vivo by restoring the translation factor EIF5AH.

# Overview of the most recent studies on spermidine



## 5. Skin and hair<sup>29,30,59</sup>

Spermidine may be a potential therapeutic agent for the treatment of atopic dermatitis. Spermidine also has a positive effect on keratin production, and influences the expression profile of hair follicles. In cell culture, it also had a proliferating effect on epithelial stem cells. Spermidine secreted by streptococci contributes to the upregulation of collagen and lipid synthesis in aged cells to restore skin structure and barrier function. Systemic and topical spermidine treatment significantly accelerates skin wound healing. Spermidine increases melanin production and could serve as a potential natural product to alleviate hypopigmentation.



## 6. Cardiovascular system<sup>31,32,33,34,35,36,37,38,60</sup>

Spermidine has a preventive effect on age-associated cardiovascular diseases. In addition, spermidine improves cellular respiration by increasing mitochondrial content in cardiac cells. Cardiac muscle cells, the so-called cardiomyocytes, which are responsible for the contraction of the heart, take up spermidine via a specific cellular transporter, whereby the positive autophagic effect can also take place in these cells. Increased NO availability in these cells results in reduced systemic inflammation. The function of blood vessels can be improved by spermidine, which can prevent atherosclerosis in the long term. Spermidine supplementation may also limit experimental abdominal aortic aneurysm formation which may make spermidine a promising treatment for this condition. Furthermore, spermidine inhibits vascular calcification in chronic kidney disease through enzyme regulation. Treatment with a mixture of trehalose, spermidine, nicotinamide, and polyphenols improves maximum walking distance (MWD) in patients with peripheral arterial disease (PAVD), with the mechanism possibly related to NOX2-mediated reduction of oxidative stress and increase of autophagic flow.

# Overview of the most recent studies on spermidine



## 7. Bones and cartilage<sup>39,40,41,42,43,61</sup>

Spermidine can increase stem cell production and has a positive effect on bone density. The natural polyamine spermidine prevents bone loss by preferentially disrupting osteoclastic activation in ovariectomized mice. In aged mice, low levels of spermidine in chondrocytes could be restored by spermidine supplementation, thereby restoring cartilage mass. By ensuring autophagic flux, spermidine contributes to the protection of chondrocytes. Spermidine could serve as a therapeutic agent for intervertebral disc degeneration (IDD)



## 8. Muscles<sup>44,45</sup>

Age-related muscle atrophy can be reduced via spermidine-induced autophagy. This protective effect has been demonstrated in mice by stress-inducible metabolic regulators.



## 9. Diabetes and obesity<sup>46,47,48,49,50,51, 65</sup>

Polyamines, such as spermidine have the potential to reduce white adipose tissue and stimulate fat oxidation. Induction of autophagy by spermidine protects against the deleterious effects of a high-fat diet in wild-type mice. In obese mice, spermidine supplementation was shown to increase glucose tolerance. Spermidine leads to regulation of lipid metabolism and improvement of antioxidant capacity and gut barrier function, and decreased expression of inflammatory cytokines and chemokines. Autophagy inducer spermidine protects against metabolic disorders during overeating.