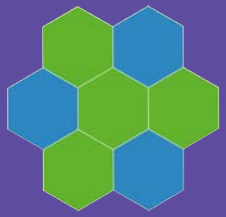
Anti-Ageing

In the Era of Cellular Medicine



ANOVA

Institute for Regenerative Medicine

Dear reader,

None of us can travel back in time. So what is anti-ageing and rejuvenation about?

To answer this question, we have to understand the processes behind ageing.

With ageing, the normal functions of our bodies work less well compared to young age. Also, diseases are more prevalent with advancing age.

Both functional deficits and diseases manifest themselves at a macroscopic level, affecting tissues and organs like skin and heart. But they originate from changes on the cellular and molecular level, resulting in genetic, metabolic, inflammatory, immunological and neoplastic pathologies.

Effective anti-ageing and rejuvenation thus requires a comprehensive approach:

- Disease prevention and early detection
- Aerobic exercise, resistance training (strength work), and stretching, flexibility, and balance
- Metabolic optimisation: Food, food additives, infusions, prescription medication
- Hormonal optimisation/ substitution
- Senescent cell removal
- Stem cell and Stem Cell Secretome Therapies
- Topical application of systemic medication (skin and hair)

In this brochure we summarise the comprehensive anti-ageing and rejuvenation treatments we have developed at ANOVA Institute for Regenerative Medicine and how we can help you stay younger and live a more active and healthy life.

We hope to welcome you soon in our clinic.

Prof. Dr. mult. Michael K. Stehling
Prof. Dr. med. Johannes Atta

Anti-Ageing and Rejuvenation

Ageing is a progressive process that gradually leads to the loss of organ functions. The resulting deficits frequently result in chronic diseases, which often occur together (multi-morbidity) and consequently increase the risk of death.

However, ageing progresses at different rates in different individuals. As a result, the biological age of an individual might differ from the chronological age in years. Why is that?

Biological age is primarily determined by the physiological ageing of the organism's cells. For humans this defines a maximum attainable life span of approximately 120 years[1].

It is, however, estimated that only 20% of the ageing process is genetically determined. Whereas 80% of ageing is caused by damaging external influences, primarily due to individual lifestyles. These harmful factors include malnutrition, consumption of addictive substances (tobacco, alcohol), and a lack of exercise, as well as physical (insomnia, shift work) and psychosocial stress.

On the up-side this means that 80% of all factors that determine ageing can be modified.

From a molecular perspective, ageing is caused by a number of highly complex mechanisms. With increasing age intrinsic repair systems, responsible for correcting errors in DNA and protein synthesis function less reliably, resulting in cumulative damage to these macromolecules, which, in turn, leads to impaired cell function.

In addition, destructive oxidation processes and the accumulation of harmful metabolic by-products from excessive nutrient supply cause further cell stress. Exogenous factors like environmental pollutants or UV light and disturbances of the neuroendocrine stress axis also contribute to attrition. Stressed and damaged somatic cells activate the immune system, which leads to a predominantly subclinical but continuous inflammatory process: inflamm-ageing.

At ANOVA Institute for Regenerative Medicine we realise that ageing and thus anti-ageing and rejuvenation is a complex, multifaceted problem. It requires a multi-disciplinary team of medical doctors, biologists, physicists, pharmacologists, nutritional experts, cosmetologists and many more to handle.

Consequently, we have made it our goal to translate the latest scientific knowledge into highly individualised treatments for individuals who want to avail themselves of effective measures to stem ageing and live a long and healthy life.

[1] Dong, Xiao, Brandon Milholland, and Jan Vijg. "Evidence for a limit to human lifespan." Nature 538.7624 (2016): 257.

Disease Prevention and Early Detection

Anti-Ageing begins with disease prevention and early detection. Modern medicine affords effective ways to detect diseases at an early, curable stage. These range from genetic and molecular diagnostics to high-resolution imaging of the whole body.

Both cardiovascular diseases and cancer are still the number one reasons for invalidity and early death. Degenerative and metabolic diseases also take their toll and cause long-term functional loss and pain, such as arthritis, cognitive impairment, reduced vision and hearing, erectile dysfunction, loss of energy, muscle- and bone mass, and many more.

The best way to avoid the negative effects of illnesses are the prevention of disease. The main approaches are common knowledge: Healthy diet, exercise, avoidance of smoking and alcohol, avoidance of stress, good sleep, and so on.

Early detection of diseases improves the chances of curing them or at least slow-down their progress. Modern medicine offers a wide range of tests to achieve this:

- Laboratory tests for metabolism, hormones, tumour markers, vitamins and minerals.
- Genetic tests revealing increased risk for certain diseases.
- Functional tests of the heart, vessels, lungs, kidneys etc.
- Imaging tests, such as whole-body MRI, coronary artery CT, low-dose CT of the lungs (for smokers), cardiovascular sonography, virtual colonoscopy, osteodensitometry, etc.

The following chapters provide information about the range of state-of-the-art diagnostic tests we use at ANOVA Institute for Regenerative Medicine to help you preserve the most valuable factors in your life: your health and vitality.

Clinical Chemistry and Laboratory Medicine

In hospitals, 70% of clinical decisions are based on laboratory testing[2]. Various specimen of blood, urine and other body fluids, as well as tissue samples can be analysed to obtain detailed information about the health of a patient to aid diagnostics, treatment and prevention of disease[3].

Clinical Pathology provides information about a wide range of disorders, often before they cause symptoms. Haematology analyses whole blood to determine its cellular composition. Clinical Biochemistry performs tests on blood serum or plasma to obtain information about organic and inorganic components such as enzymes for the assessment of organ function, blood lipids and sugar as well as hormones but also about coagulation and toxins such as drugs and heavy metals. Microbiology, Parasitology and Virology provide information about infectious diseases from samples of blood, urine, sputum, faeces, and cerebrospinal and synovial fluid, or infected tissues. Immunology/Serology employs antigen-antibody interaction as a diagnostic tool. Surgical pathology, Histopathology and Cytopathology examine organs, tissues and cells obtained from the body, e.g. by biopsy, to determine the presence of inflammation, cancer, and other pathological conditions.

Genetic Testing

Molecular Diagnostics and Cytogenetics includes specialised tests involving DNA analysis. These tests provide information in cases of prenatal diagnosis, the early detection of cancers, to assess a patient's risk for certain diseases before they cause symptoms, establishing the diagnosis of a disease that is already present, or predicting whether a particular medication will be effective to treat the patient's condition or will cause dangerous side-effects.

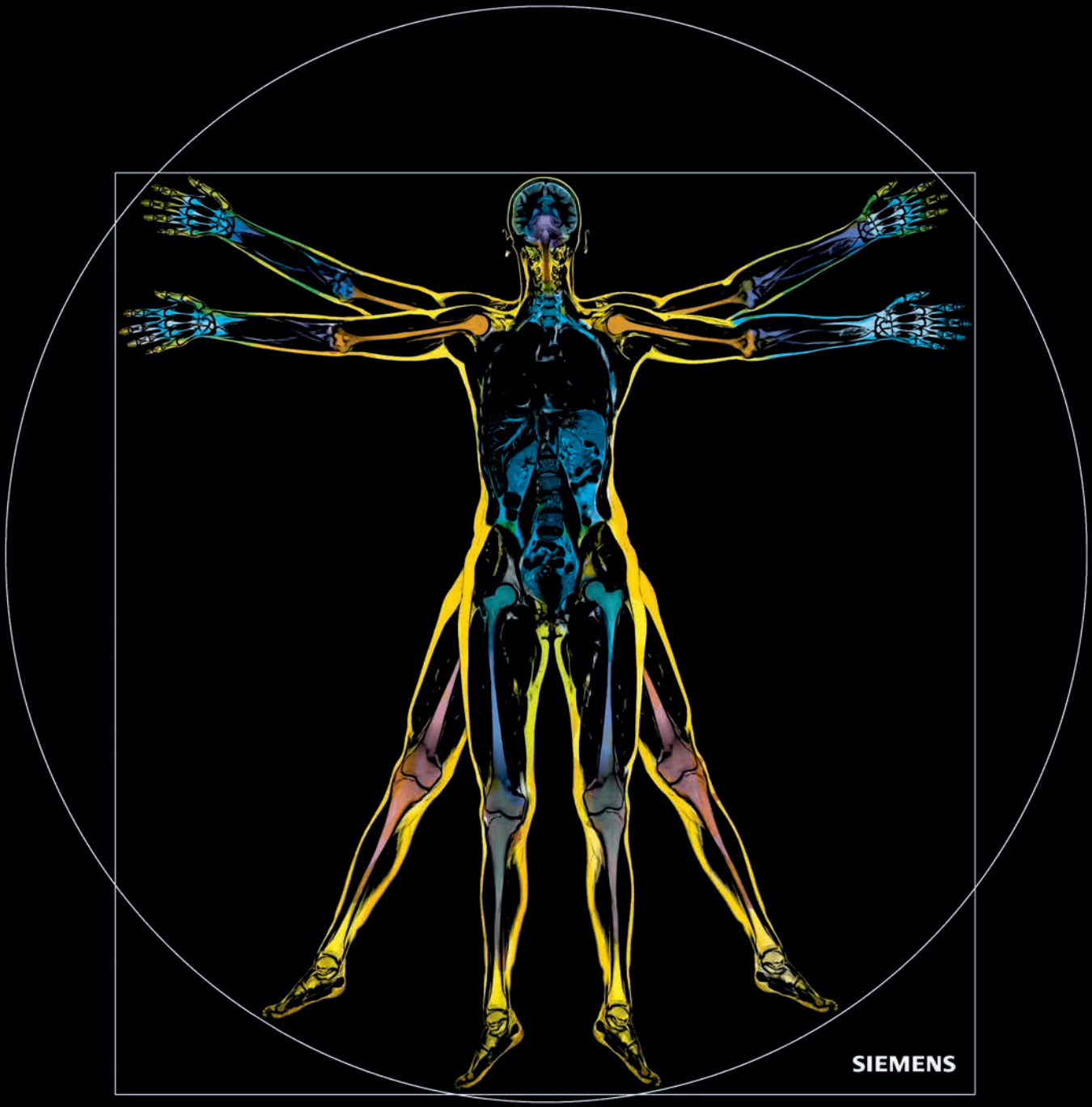
Over 2,000 tests are available today. They can be carried out on small samples of blood or saliva.

People have many different reasons for being tested or not being tested. For some, it is important to know whether a disease can be prevented or treated if a test is positive. In some cases, there is no treatment. But test results might help a person make life decisions, such as family planning or insurance coverage.

At ANOVA Institute for Regenerative Medicine we use many different tests to detect diseases early, before they become clinically apparent. Our clinical specialists will explain to you which tests are suitable for your condition and what the results imply.

[2] https://health.usnews.com/health-news/patient-advice/articles/2015/01/30/hospital-labs-behind-the-scenes

[3] Farr, J. Michael, and Laurence Shatkin. Best jobs for the 21st century. Indianapolis, IN: Jist Works, 2009. ISBN 978-1-56370-961-6


SIEMENS

Whole-Body Imaging

Since the invention of Magnetic Resonance Imaging (MRI) in the 1970ies, whole-body imaging has developed into a powerful tool for the structural and functional analysis of the human body. MRI provides multi-parametric data sets, which can provide detailed information of all tissues and organs and can be employed for the early detection and staging of diseases long before they become clinically apparent.

Whole-body MRI can detect tumours, degenerative changes of joints and the spine, atherosclerotic narrowing of vessels and the resulting lack of blood supply to the heart, brain or kidneys, early neurodegenerative changes of the brain, problems of the liver, pancreas and gastro-intestinal tract – to name just a few.

At ANOVA Institute of Regenerative Medicine we use modern imaging technologies to elucidate even the minutest changes in our patients' bodies – to stem the progress of age and disease:

- Calcium Scoring:
  The number one predictor of heart attacks
- Virtual Colonoscopy:
  Colon cancer screening without the need for endoscopy
- Low-dose lung screening:
  Early detection of lung cancer for smokers
- MR[4] Mammography:
  The only effective breast cancer screening modality
- MR Angiography:
  Evaluation of vessels and blood supply throughout the body
- PET[5]-Scan:
  Metabolic imaging for cancer and neurodegenerative diseases
- Prostate-MRI:
  Early detection of prostate cancer for men
- Cardio-MRI:
  Comprehensive assessment of the heart
- CT[6]-Osteodensitometry:
  Precise assessment of bone mineralisation

These are just a few examples. At ANOVA Institute for Regenerative Medicine we provide the full range of state-of-the-art imaging either within our clinic or through one of our associated clinical partner institutions. Our specialists will advise you, which tests are most appropriate for you and your specific health concerns.

[4] MR(I) = Magnetic Resonance (Imaging)
[5] PET = Positron-Emission-Tomography
[6] CT = Computed Tomography

Determination of Biological Age and Ageing

At ANOVA Institute for Regenerative Medicine we endeavour to slow ageing. But how do we recognise ageing? Apart from the obvious physical signs age can be measured. Not only in years, but with biomarkers, which allow the "true" biological age of an individual to be estimated. By comparison with the chronological age, this provides insights into an individual's ageing process and the speed with which it progresses. The same biomarkers make it possible to test whether anti-ageing interventions and therapies are conducive to prolonging life expectancy.

DNA-Methylation - The Epigenetic Clock

Ageing is associated with epigenetic modifications which are highly reproducible[7]. By analysing a wide range of DNA-methylation profiles of the genome, an Epigenetic-Ageing-Signature can be determined. Integrating the degree of DNA-methylation of these sites into a mathematical model, the biological age of the donor can be predicted with an accuracy of 5 years (mean average deviation from chronological age). The deviation from chronological age can, amongst other factors, be attributed to gender, disease and life-style parameters.

Biological age can be predicted both from blood and samples from the mucosa of the mouth (buccal swabs).

Whilst buccal swabs are a totally non-invasive way to harvest DNA, these specimens are a heterogeneous mixture of buccal epithelial cells and 5 - 60% of leukocytes (white blood cells). By taking the cellular composition of these buccal swabs into consideration, epigenetic age predictions can be rendered more precise[8].

Telomeres - The Biological Clock of Each Somatic Cell

Telomeres are repetitive DNA sequences on the terminal ends of chromosomes (Fig. X.1). They protect DNA from enzymatic and structural degradation as well as exchange of genetic material with other chromosomes.

Telomeres shorten with each DNA replication. When the telomeres reach a critical length after multiple cell divisions, the affected cells stop dividing (Fig. X.2). These cells enter a dormant state of replicative senescence or die through the process of apoptosis - programmed cell death.

[7] Weidner, Carola Ingrid, et al. "Aging of blood can be tracked by DNA methylation changes at just three CpG sites." Genome biology 15.2 (2014): R24.

[8] Eipel, Monika, et al. "Epigenetic age predictions based on buccal swabs are more precise in combination with cell type-specific DNA methylation signatures." Aging (Albany NY) 8.5 (2016): 1034.

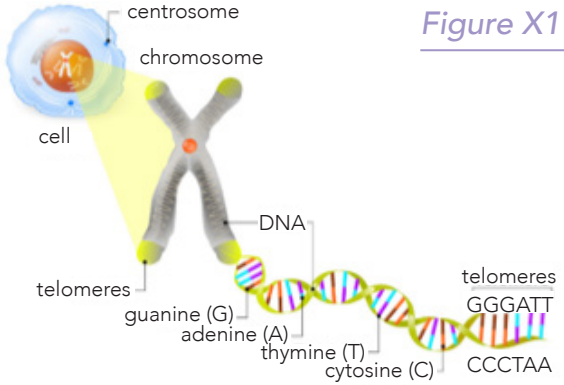


Figure X1

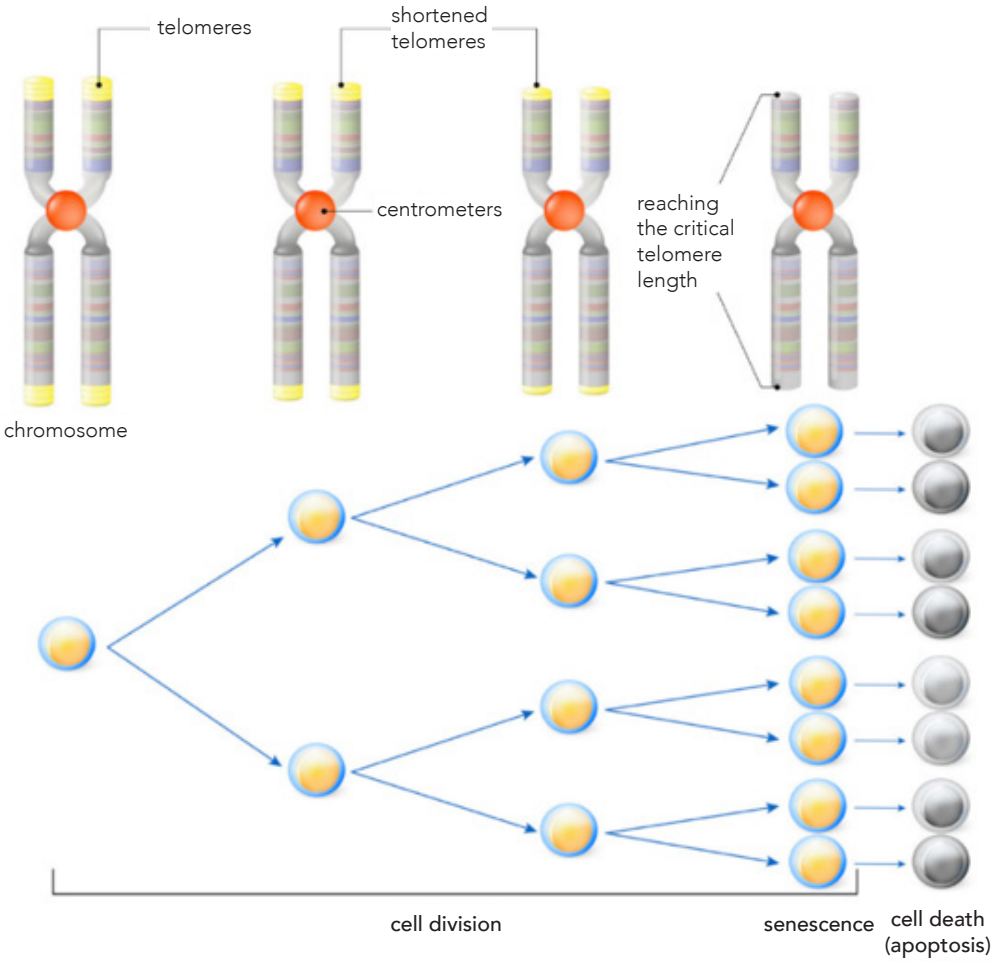


Figure X2

The scientist Leonhard Hayflick found that human cells can undergo a maximum of 50 to 60 cell divisions ("Hayflick limit")[9]. But shrinkage of the telomeres may also lead to genomic instability caused by fusion of the ends of linear chromosomes, an initial step in the development of certain cancers.

In our bodies cells responsible for the regeneration of tissues exhibit increased division activity and thus are more affected by telomere shortening. This is why ageing is most evident in tissues such as the skin and hair, but also the blood and gastrointestinal mucosa. Various studies show a clear correlation between chronological age and telomere shortening[10, 11, 12].

Ageing of the Immune System – Immune Senescence

The cells of the immune system - especially the B and T lymphocytes - also proliferate as a result of immunostimulation induced by infection with viruses and bacteria or immunological malfunction such as allergies, autoimmune diseases and chronic infection. Consequently they experience a marked decrease in telomere length with increasing age and frequent stimulation[13]. This process is called "immune senescence" and leads to less an effective immune defence[14, 15].

The consequences of immune senescence are far-reaching [16, 17]. With increasing age, susceptibility to new infections increases and old infections (e.g. varicella-zoster) can flare-up. Not to mention cancer can grow and spread faster due to a weakened immune system. Furthermore, ageing immune cells release a pro-inflammatory secretome, thus supporting chronic inflammation in the body (inflamm-ageing)[18].

At ANOVA Institute for Regenerative Medicine we employ tests to determine the biological age of our patients for many reasons: To determine the status-quo of an individual at the time of testing, to make predictions of an individual's life expectation and specific corrective measures that should be implemented to maintain health and promote longevity.

[9] Hayflick, Leonard. "The limited in vitro lifetime of human diploid cell strains." Experimental cell research 37.3 (1965): 614-636.
[10] Butler, Merlin G., et al. "Comparison of chromosome telomere integrity in multiple tissues from subjects at different ages." Cancer genetics and cytogenetics 105.2 (1998): 138-144.
[11] Lindsey, Janet, et al. "In vivo loss of telomeric repeats with age in humans." Mutation Research/DNAging 256.1 (1991): 45-48.
[12] Aubert, G. "Lansdorp pM. Telomeres and aging. 37." Physiol Rev 88 (2008): 557-79.
[13] Daniali, Lily, et al. "Telomeres shorten at equivalent rates in somatic tissues of adults." Nature communications 4 (2013): 1597.
[14] Castelo-Branco, Camil, and Iris Soveral. "The immune system and aging: a review." Gynecological Endocrinology 30.1 (2014): 16-22.
[15] Desai, Anjali, Annabelle Grolleau-Julius, and Raymond Yung. "Leukocyte function in the aging immune system." Journal of leukocyte biology 87.6 (2010): 1001-1009.
[16] Frasca, Daniela, and Bonnie B. Blomberg. "Aging, cytomegalovirus (CMV) and influenza vaccine responses." Human vaccines & immunotherapeutics 12.3 (2016): 682-690.
[17] Mazzola, Paolo, et al. "Aging, cancer, and cancer vaccines." Immunity & Ageing 9.1 (2012): 4.
[18] Baylis, Daniel, et al. "Understanding how we age: insights into inflammaging." Longevity & healthspan 2.1 (2013): 8.


HIIT
WORKOUT

Anti-Ageing Workout - According to Science

Scientific research from Germany indicates that endurance training (ET) and high intensity interval training (HIIT) workouts may reduce signs of ageing at the cellular level.

In a recent study published in the European Heart Journal[19] scientists compared the effects of three different types of exercise – ET, HIIT and resistance training (RT) –on the ageing of cells in the human body. They found that both ET and HIIT slowed cellular ageing - or even reversed it; RT did not.

Chromosomes, which carry genetic information in the form of DNA, contain a repetitive DNA sequence at their end, called a telomere, which plays a crucial role in cell division. As we grow older, the shortening of telomeres constitutes an important molecular mechanism for cell ageing, eventually leading to cell death. The enzyme telomerase can counteract this shortening and can even extend the length of the telomeres.

The research has shown that endurance training and HIIT can increase telomerase activity two- to three-fold with a resulting significant increase in telomere length.

The scientists assume that "a possible mechanism that might explain why endurance and high intensity training could increase telomere length and telomerase activity is that these types of exercise affect levels of nitric oxide in the blood vessels, contributing to the changes in the cells[19]".

Resistance training, such as weightlifting, however still plays an important role in workouts for anti-ageing. The microscopic damage resistance training inflicts on muscles - and which is felt as sore muscles after a strenuous workout - increases the levels of growth hormones (somatotropic hormone - STH) and testosterone in the body, resulting in increased muscle mass and decreases body fat. This in turn leads to improved glucose metabolism and can eliminate pre-diabetic metabolic dysregulation. It also improves bone mineralisation and thus fights age-related osteoporosis.

"From an evolutionary perspective, endurance and high intensity training may mimic the advantageous travelling and fight or flight behaviour of our ancestors better than strength training[19]" said Dr. Werner, one of the scientists conducting the study.

[19] Werner, Christian M., et al. "Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study." European heart journal 40.1 (2018): 34-46.

Nutritional Supplements and Prescription Drugs for Anti-Ageing

Dietary supplements[20] are products which complement the diet when taken orally as a pill, capsule, tablet, or liquid[21]. A supplement can provide natural or synthetic nutrients, in combination or individually. Typical compounds are vitamins, nutritionally essential minerals, amino acids and fatty acids, fibre, and proteins, but may also comprise substances such as plant pigments or polyphenols, which are believed to have positive effects on health, as well as collagen from animal sources. Probiotics contain live bacteria as an ingredient. They may also contain synthetic copies of naturally occurring substances, such as melatonin.

Vitamins

Vitamins are required as vital nutrients in limited amounts[22] because the human body cannot synthesize them in sufficient quantities. Humans have to consume thirteen "essential" vitamins in their diet: vitamins A, B1 (thiamine), B2 (riboflavin), B3 (niacin) and B5 (pantothenic acid), vitamin group B6 (pyridoxal 5α-phosphate), vitamins B7 (biotin), B9 (folate), B12 (cobalamin), C (ascorbic acid), vitamin group D (secosteroids), E (tocopherols and tocotrienols) and K (vitamins K1 and K2)[23].

Minerals

The essential dietary minerals for humans, listed by decreasing "adequate daily intake" are potassium, sodium, chlorine, calcium [24], magnesium, phosphorus, iron, zinc, manganese, copper, iodine, chromium, molybdenum, selenium [25] and cobalt (the last as a component of vitamin B12). Whilst calcium being important for the bones is common knowledge, it is less well known that magnesium fends off cardiovascular diseases, asthma and migraines, that zinc boosts the immune system and selenium helps to prevent cancer.

Proteins and Amino Acids

Proteins consist of a chain of amino acids. Nine amino acids cannot be synthetized in the human body and are thus considered essential for humans because:

"The International Olympic Committee recommends protein intake targets for both strength and endurance athletes of about 1.2 - 1.8 g/kg body mass per day"[26]. "In elderly people, supplementation with just leucine resulted in a modest (0.99 kg) increase in lean body mass"[27].

[20] Dietary Supplement Labels: Key Elements Office of Inspector General, Depart of Health and Human Services. 2003.

[21] National Institutes of Health. "Dietary supplements: Background information." Office of Dietary Supplements Fact Sheet. Washington, DC: National Institutes of Health, US Department of Health and Human Services (2011).

[22] LIEBERMAN, Shari, and Nancy BRUNING. "The Real Vitamin & Mineral Book-Going beyond the RDA for Optimum Health; Avery Publ." Group (1990): 142.

[23] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). "Scientific Opinion in relation to the authorisation procedure for health claims on calcium and vitamin D and the reduction of the risk of osteoporotic fractures by reducing bone loss pursuant to Article 14 of Regulation (EC) No 1924/2006." EFSA Journal 8.5 (2010): 1609.

[24] Food and Drug Administration, HHS. "Food labeling: health claims; calcium and osteoporosis, and calcium, vitamin D, and osteoporosis. Final rule." Federal register 73.189 (2008): 56477.

[25] US Food and Drug Administration. "Qualified health claims: letter of enforcement discretion–nuts and coronary heart disease." Rockville, MD: US Food and Drug Administration (2003): 1-4.

Supplements containing the amino acid arginine, which can be synthetised in the human body, can be helpful for the synthesis of nitric oxide, and thus have a cardio-protective effect. A look into the scientific literature confirmed its effect on lowering blood pressure[28]. Arginine also decreases cholesterol and improves erectile function in men. Other amino acids, such as tyrosine, have been shown to have anti-depressant activity, whilst glutathione and N-acetyl-cysteine (NAC) are potent anti-oxidants, NAC in addition being one of the few medications which can lower lipoprotein(a), a promotor of atherosclerosis.

Essential Fatty Acids

Fatty acids are strings of carbon (C) atoms of differing lengths. In saturated fatty acids all carbon atoms are linked by single bonds (C-C), unsaturated fatty acids contain one double bond (C=C), contain polyunsaturated fatty acids several double bonds. Two types of polyunsaturated fatty acids are "essential", since they cannot be synthesised by the human body: alpha-linolenicacid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid[29]. Other omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can be synthetised in the body by elongation of ALA. Food sources for ALA are plant oils, particularly oils from seeds and nuts. DHA and EPA are contained in higher amounts in oceanic fish, with krill oil, fish oiland marine algae extracts being typical dietary supplement sources.

"The European Food Safety Authority (EFSA) identifies 250 mg/day for a combined total of EPA and DHA as Adequate Intake, with a recommendation that women pregnant or lactating consume an additional 100 to 200 mg/day of DHA."[30]

"In 2017, the American Heart Association issued a science advisory stating that it could not recommend use of omega-3 fish oil supplements for primary prevention of cardiovascular disease or stroke, although it reaffirmed supplementation for people who have a history of coronary heart disease."[31]

[26] Thomas, D. Travis, Kelly Anne Erdman, and Louise M. Burke. "Position of the Academy of Nutrition and Dietetics, Dietitians of Canada, and the American College of Sports Medicine: nutrition and athletic performance." Journal of the Academy of Nutrition and Dietetics 116.3 (2016): 501-528.

[27] Komar, B., L. Schwingshackl, and Georg Hoffmann. "Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis." The journal of nutrition, health & aging 19.4 (2015): 437-446.

[28] Dong, Jia-Yi, et al. "Effect of oral L-arginine supplementation on blood pressure: a meta-analysis of randomized, double-blind, placebo-controlled trials." American heart journal 162.6 (2011): 959-965.

[29] Omega−3 Fatty Acids and Health: Fact Sheet for Health Professionals. US National Institutes of Health, Office of Dietary Supplements. 2 November 2016. Retrieved 5 April 2017

[30] European Food Safety Authority (EFSA). "Dietary Reference Values for nutrients Summary report." EFSA Supporting Publications 14.12 (2017): e15121E.

[31] Siscovick, David S., et al. "Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association." Circulation 135.15 (2017): e867-e884.

Natural Products

Dietary supplements can also be obtained from plants or their extracts, alike algae, fungi or animals. Examples of these are resveratrol, ginkgo biloba, ginseng, cranberry, St. John's wort, glucosamine and collagen[32]. Many of these substances have been employed in herbalism and traditional medicine for centuries. A number of natural products have been scientifically studied for their anti-cancer effects, such as gingerol[33], curcumin[34], and boswellic acid[35], to name just a few.

Probiotics

The human colon – the large intestine – hosts over 1,000 different species of microorganisms. Most of them are bacteria, numbering in the tens of trillions[36] "Probiotic" - in the context of dietary supplements - refers to the concept that the ingestion of specific yeast or bacteria can influence the composition of the colon's microbiome with resulting health benefits; amongst those are the maintenance of gastrointestinal health[37], e.g. by reducing constipation or diarrhoea, and improving immune health.

Probiotic supplements are generally considered safe as long as antibiotic resistant bacteria are reliably excluded[38].

Whilst most nutritional supplements are available "over the counter" without prescription in most countries, there is a controversy about their effectiveness and whether they should be taken as mono-constituent substances, containing only one type of chemical substance, or multi-constituent substances, which might provide synergistic effects or UVCBs (Unknown or Variable composition, Complex reaction products or Biological materials), such as extracts from plants, which contain the natural composition required for the full effectiveness of the supplement.

[32] Natural and Non-prescription Health Products. Government of Canada. 2018.
[33] De Lima, Rosália Maria Tôrres, et al. "Protective and therapeutic potential of ginger (Zingiber officinale) extract and [6]-gingerol in cancer: A comprehensive review." Phytotherapy research 32.10 (2018): 1885-1907.
[34] Liu, Hui-Tien, and Yuan-Soon Ho. "Anti-cancer effect of curcumin on breast cancer and stem cells." Food Science and Human Wellness 7.2 (2018): 134-137.
[35] Li, Wan, et al. "3-O-acetyl-11-keto-β-boswellic acid exerts anti-tumor effects in glioblastoma by arresting cell cycle at G2/M phase." Journal of Experimental & Clinical Cancer Research 37.1 (2018): 132.
[36] Thursby, Elizabeth, and Nathalie Juge. "Introduction to the human gut microbiota." Biochemical Journal 474.11 (2017): 1823-1836.
[37] Durchschein, Franziska, Wolfgang Petritsch, and Heinz F. Hammer. "Diet therapy for inflammatory bowel diseases: The established and the new." World journal of gastroenterology 22.7 (2016): 2179.
[38] Doron, Shira, and David R. Snydman. "Risk and safety of probiotics." Clinical Infectious Diseases 60.suppl_2 (2015): S129-S134.

Will Metformin Become the First Anti-Ageing Drug?[39]

A group of researchers is currently trying to validate Metformin as the first-ever anti-ageing medication[40]. Metformin is a regularly prescribed drug for diabetic patients; in England it has been in use since 1958. Naturally with a drug that has been in use for so long, Metformin has a track record of safety and effectiveness at routine doses of up to 2,000 mg daily[41].

However, Metformin appears to have properties that extend far beyond blood sugar control. It can stop and even reverse many of the factors that are involved in the process of ageing[42]. It can, for instance, protect against chronic inflammation, DNA damage, and poor mitochondrial function. Metformin has also been shown to facilitate DNA repair processes, which can be an important factor for cancer prevention.

Metformin can also help increase the production of longevity-promoting signaling molecules in cells, such as mTOR and AMPK—all, which play a role in the reduction of fat and sugar storage and increasing of youthful functioning at the cellular level[11, 12]. Recent scientific work has shown that by activating AMPK, whose activity declines with age, Metformin specifically impacts lifespan. Most impressively, patients with diabetes taking Metformin were shown to live 15% longer than individuals without diabetes[43].

The drug also plays an essential role in preventing age-related disorders. Research showed that patients taking Metformin have a 46% reduction in risk of developing head and neck cancers[44], other research showed that patients taking Metformin experienced a 55% decrease in the risk of stomach cancer compared to the control group[45]. But Metformin not only has the potential to reduce the risk of developing cancer, it might also improve survival in patients who already have cancer.

A review study which looked into 27 clinical trials with more than 24,000 patients found that in people with early-stage cancers of the rectum and colon, the use of Metformin improved recurrence-free survival by 37%, overall survival by 31%, and cancer-specific survival by 42%[46]. The same study reported similar effects in men with early-stage prostate cancer, with the detection of increased recurrence-free survival by 17%, overall survival by 18%, and cancer-free survival by 42% in patients who took Metformin[47].

[39] Adapted from: Life Extension, 3600 West Commercial Boulevard, Fort Lauderdale, FL 33309
[40] Barzilai, Nir, et al. "Metformin as a tool to target aging." Cell metabolism 23.6 (2016): 1060-1065.
[41] Available at: https://www.drugs.com/dosage/metformin.html.
[42] Martin-Montalvo, Alejandro, et al. "Metformin improves healthspan and lifespan in mice." Nature communications 4 (2013): 2192.
[43] Bannister, CA 1., et al. "Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls." Diabetes, Obesity and Metabolism 16.11 (2014): 1165-1173.
[44] De Oliveira Figueiredo, Rejane Augusta, et al. "Diabetes mellitus, metformin and head and neck cancer." Oral oncology 61 (2016): 47-54.
[45] Tseng, Chin-Hsiao. "Metformin reduces gastric cancer risk in patients with type 2 diabetes mellitus." Aging (Albany NY) 8.8 (2016): 1636.
[46] Coyle, C., et al. "Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis." Annals of Oncology 27.12 (2016): 2184-2195.

Metformin prevents cardiovascular disease: Amongst the causes of cardiovascular disease, atherosclerosis is the main problem. It is promoted by the accumulation of LDL cholesterol in arterial walls, with resultant damage to the endothelium, the inner lining of the walls[48].

Metformin can prevent these early steps in atherosclerosis. By activating AMPK, Metformin decreases LDL oxidation and thus endothelial dysfunction, which reduces the conversion of harmless monocytes into fat-laden macrophages, thus reducing their harmful accumulation in vessel walls[49]. It also helps cholesterol export out of macrophages, and suppresses the inflammation they normally produce[50].

In a recent study in human subjects, heart attack patients taking Metformin had a 75% reduction in the risk of dying after 30 days, and a 68% reduction in their risk of dying 12 months after the attack[51]. Other studies have additionally demonstrated that the drug reduces the risk of stroke, heart attack, atrial fibrillation (an arrhythmia), systolic blood pressure[29], and death from all causes[52].

Metformin as a Neuroprotectant: But Methformin may also protect against neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. Studies have shown that it reduces levels of an enzyme that generates beta-amyloid proteins[53], decreases the harmful effect of beta-amyloid on brain cell function[54], reduces levels of alpha-Synuclein, another protein that accumulates and causes damage in Parkinson's disease[55], prevents the loss of dopamine-producing brain cells[56] and improves motor coordination[45, 57] in a model of Parkinson's disease.

---

[47] Anisimov, Vladimir N. "Metformin for cancer and aging prevention: is it a time to make the long story short?." Oncotarget 6.37 (2015): 39398.
[48] Dong, Yunzhou, et al. "Activation of AMP-activated protein kinase inhibits oxidized LDL-triggered endoplasmic reticulum stress in vivo." Diabetes 59.6 (2010): 1386-1396.
[49] Vasamsetti, Sathish Babu, et al. "Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: potential role in atherosclerosis." Diabetes 64.6 (2015): 2028-2041.
[50] Wan, Xinyi, et al. "5'-AMP–Activated Protein Kinase–Activating Transcription Factor 1 Cascade Modulates Human Monocyte–Derived Macrophages to Atheroprotective Functions in Response to Heme or Metformin." Arteriosclerosis, thrombosis, and vascular biology 33.11 (2013): 2470-2480.
[51] Abualsuod, Amjad, et al. "The effect of metformin use on left ventricular ejection fraction and mortality post-myocardial infarction." Cardiovascular drugs and therapy 29.3 (2015): 265-275.
[52] Anabtawi, Abeer, and John M. Miles. "Metformin: nonglycemic effects and potential novel indications." Endocrine Practice 22.8 (2016): 999-1007.
[53] Wang, Man, et al. "Metformin for treatment of antipsychotic-induced weight gain: a randomized, placebo-controlled study." Schizophrenia research 138.1 (2012): 54-57.
[54] Luchsinger, José A., et al. "Metformin in amnestic mild cognitive impairment: results of a pilot randomized placebo controlled clinical trial." Journal of Alzheimer's Disease 51.2 (2016): 501-514.
[55] Pérez-Revuelta, B. I., et al. "Metformin lowers Ser-129 phosphorylated α-synuclein levels via mTOR-dependent protein phosphatase 2A activation." Cell death & disease 5.5 (2014): e1209.
[56] Bayliss, Jacqueline A., et al. "Metformin prevents nigrostriatal dopamine degeneration independent of AMPK activation in dopamine neurons." PLoS One 11.7 (2016): e0159381.
[57] Patil, S. P., et al. "Neuroprotective effect of metformin in MPTP-induced Parkinson's disease in mice." Neuroscience 277 (2014): 747-754.

Prescription Drugs for Anti-Ageing

Drugs that target the mTOR pathway could one day become widely used to slow ageing and reduce age-related pathologies in humans[58]. Currently, Metformin and rapamycin are under investigation as the first anti-ageing drugs. Another class of drugs, such as the antibiotic Azithromycin, and Dasatinib, a tyrosine-kinase inhibitor, are currently investigated for their potential to remove senescent cells from the body. But many others prescription medications also have life prolonging effects: Aspirin has reduces blood clotting but might also prevent colon cancer, statins reduce cholesterol and prevent cardiovascular diseases. Deprenyl, an Anti-Parkinson's Medication, has been shown to slow ageing of the brain[59] even in very small doses.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) is employed to treat symptoms associated with the lack of sexual hormones: oestrogen and progesterone in women during menopause[60], lower testosterone levels in men with increasing age[61].

The symptoms associated with low levels of sexual hormones can include fatigue, hot flashes, erectile dysfunction in men and vaginal dryness and atrophy in women, accelerated skin ageing, metabolic dysregulation, decreased muscle mass, and bone loss.

In men with low testosterone levels, HRT lowers the risk of heart disease, improves metabolism and decreases overall morbidity. Similar beneficial effects have been reported with HRT in women.

Monitoring of side effects during HRT, however, is recommended. In women, breast cancer, in men, prostate cancer should be excluded by imaging and laboratory tests.

At ANOVA Institute for Regenerative Medicine our clinical experts will advise you which nutritional additives and prescription drugs can help you prevent diseases, optimise your metabolism and immune system, increase your strength and vigour, optimise your body composition, and live a long and healthy life.

[58] Johnson, Simon C., Peter S. Rabinovitch, and Matt Kaeberlein. "mTOR is a key modulator of ageing and age-related disease." Nature 493.7432 (2013): 338.

[59] Miklya, I. "The significance of selegiline/(−)-deprenyl after 50 years in research and therapy (1965–2015)." Molecular psychiatry 21.11 (2016): 1499.

[60] Stuenkel, Cynthia A., et al. "Treatment of symptoms of the menopause: an endocrine society clinical practice guideline." The Journal of Clinical Endocrinology & Metabolism 100.11 (2015): 3975-4011.

[61] Bhasin, Shalender, et al. "Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline." The Journal of Clinical Endocrinology & Metabolism 103.5 (2018): 1715-1744.

Probiotics can do many things to improve your gut health. For instance, they may also indirectly have a positive effect on your brain, too.

Recent scientific research has shown that the gut and brain are well connected, this connection is called the gut-brain axis. The two are in permanent communication via biochemical signaling between the nervous system in the digestive tract, called the enteric nervous system, and the central nervous system. The primary information connection between the gut and the brain is the vagus nerve.

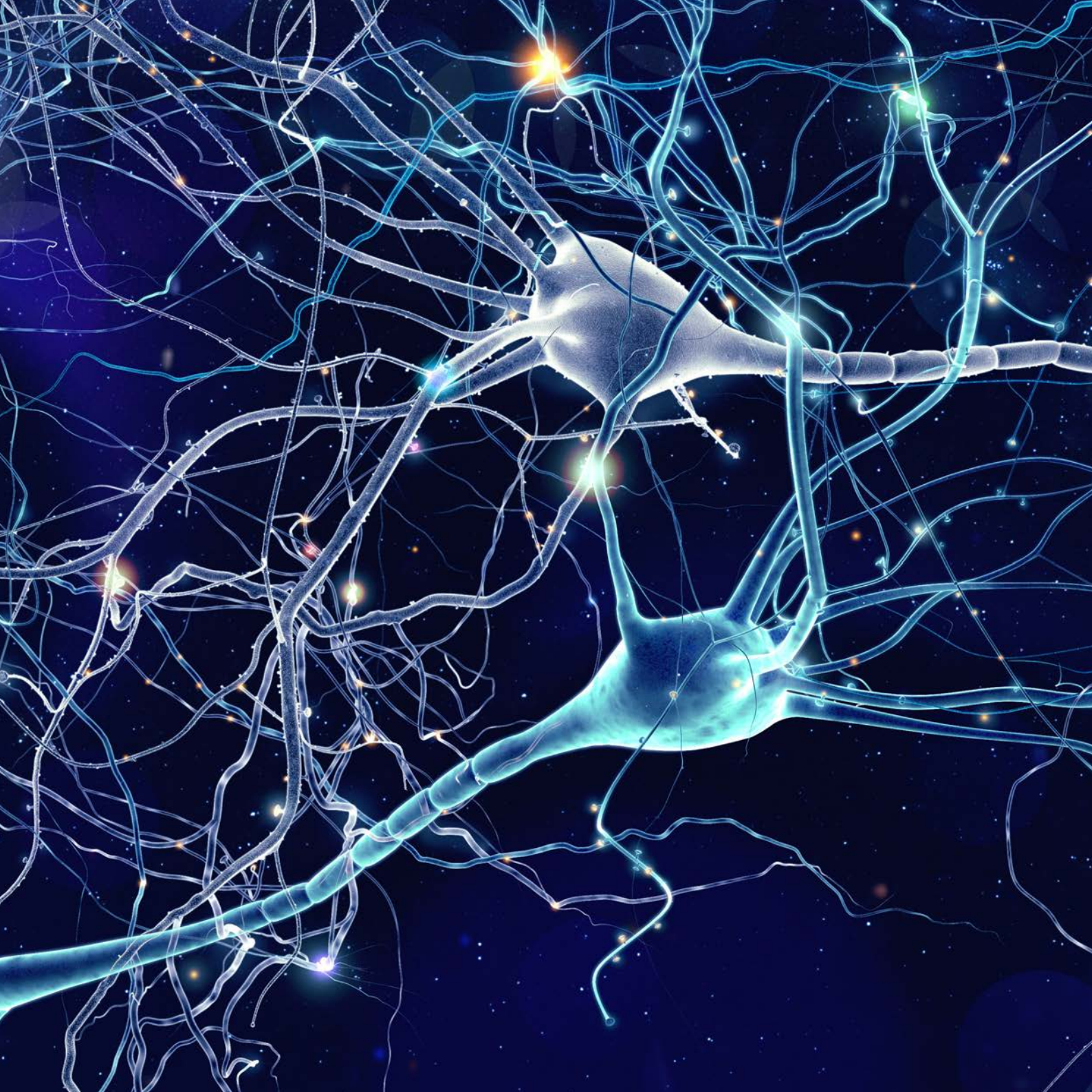
The gut is regularly being called the "second brain", because it produces many neurotransmitters which are also produced in the brain, such as serotonin, dopamine, and gamma-aminobutyric acid.

When your brain senses trouble, it sends warning signals to the gut, which is why stressful events can cause digestive problems which manifest in a nervous or upset stomach. Flares of gastrointestinal issues like irritable bowel syndrome (IBS) or chronic constipation may trigger or enhance anxiety or depression in the brain.

The brain-gut axis works in other areas as well. For example, the gut helps regulate appetite by telling the brain when it is time to stop eating. About 20 minutes after the last bite, gut microbes produce proteins that can suppress appetite, which coincides with the time it takes people to begin to feel full.

New research suggests that probiotics may help boost mood and cognitive functions which at the same time decreases anxiety and stress. For example, a study published online in 2016 found that patients with Alzheimer's Disease who took milk made with four probiotic bacteria species for 12 weeks scored better on a test which measures cognitive impairment compared to those who drank regular milk.

It is too early to determine the exact role probiotics play in the gut-brain axis, because research in this area is still ongoing. But current results imply that probiotics may not only support a healthier gut, but a healthier brain as well.



The Role of Stem Cells in Anti-Ageing

Stem cells are the essential building blocks from which all tissues and organs of the human body are derived. They have the unique ability to regenerate and rejuvenate by replacing damaged cells. Whilst stem cells are found primarily in organs where cells are lost and replaced at high rates, such as the blood-forming bone marrow, gut and skin/hair, all organs contain organ specific stem cells, even the brain. Most stem cells are dormant. When damage occurs, cytokines and micro-vesicles released by damaged tissues can trigger them into action.

Mesenchymal Stem Cells (MSCs) are a particular type of adult stem cells which are easy to harvest from the subcutaneous fat or bone marrow. They are less controversial than embryonic stem cells. MSCs are currently seen as a useful therapeutic source for many pathological conditions and disorders. These stem cells are a core biofactor in regeneration of skin, muscle, cartilage, and bone.

The restorative, anti-inflammatory, and immunomodulatory qualities of stem cells have been shown effective for the treatment of a wide range of pathological conditions, including cardiovascular[62] and neurologic diseases, such as stroke[63], spinal cord injuries[64], and Parkinson's disease[65]; autoimmune diseases such as multiple sclerosis[66] and systemic lupus erythematosus[67] as well as the healing of wounds[68] and the repair of cartilage defects[69] in osteoarthritis.

Over the past few years, particular focus was put on the use of stem cell-based therapies in urology, especially for the treatment of erectile dysfunction (ED)[70]. Many preclinical studies have explored the utility of stem cells, particularly Bone Marrow Stem Cells (BMSC) and Adipose-Derived Stem Cells (ADSCs) for the treatment of ED in animal models, summarised by Soebadi et al.[71] in 2016.

[62] Chen, Shaoliang, et al. "Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery." The Journal of invasive cardiology 18.11 (2006): 552-556.

[63] Bang, Oh Young, et al. "Autologous mesenchymal stem cell transplantation in stroke patients." Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 57.6 (2005): 874-882.

[64] Pal, Rakhi, et al. "Ex vivo-expanded autologous bone marrow-derived mesenchymal stromal cells in human spinal cord injury/paraplegia: a pilot clinical study." Cytotherapy 11.7 (2009): 897-911.

[65] Venkataramana, Neelam K., et al. "Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease." Translational Research 155.2 (2010): 62-70.

[66] Harris, Violaine K., et al. "Phase I trial of intrathecal mesenchymal stem cell-derived neural progenitors in progressive multiple sclerosis." EBioMedicine 29 (2018): 23-30.

[67] Sun, Lingyun, et al. "Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans." Stem cells 27.6 (2009): 1421-1432.

[68] Dash, Nihar Ranjan, et al. "Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells." Rejuvenation research 12.5 (2009): 359-366.

[69] Wakitani, Shigeyuki, et al. "Safety of autologous bone marrow derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months." Journal of Tissue Engineering and Regenerative Medicine 5.2 (2011): 146-150.

[70] Khera, Mohit, Maarten Albersen, and John P. Mulhall. "Mesenchymal stem cell therapy for the treatment of erectile dysfunction." The journal of sexual medicine 12.5 (2015): 1105-1106.

[71] Soebadi, M. Ayodhia, et al. "Advances in stem cell research for the treatment of male sexual dysfunctions." Current opinion in urology 26.2 (2016): 129-139.

Anti-Wrinkle Effect of Adipose-Derived Stem Cells: Activation of Dermal Fibroblast by Secretory Factors

Ultraviolet-B rays (UVB) of sunlight induce wrinkles in human skin. Scientists from Korea found that the antioxidant and wound-healing effects of Adipose-Derived Stem Cells (ADSC) can reduces these wrinkles.

Whilst the direct injection of stem cells derived from subcutaneous fat into the skin reduced wrinkles and increased dermal thickness and collagen content, in another study they showed that the MSC Secretome was the active agent. In human dermal fibroblasts (HDF) exposed to UVB MSC Secretome decreased the UVB-induced apoptotic cell death.

In addition, MSC Secretome increased the protein expression of collagen type I and decreased the protein level of matrix mataloproteinase 1 in HDF, which may account for the increased collagen contents in the dermis.

These results indicate that MSC Secretome derived from subcutaneous fat is effective for reducing UVB-induced wrinkles, and the anti-wrinkle effect is mainly mediated by reducing UVB-induced apoptosis and stimulating collagen synthesis of HDF.

Kim, Won-Serk, et al. "Antiwrinkle effect of adipose-derived stem cell: activation of dermal fibroblast by secretory factors." Journal of dermatological science 53.2 (2009): 96-102.

Mesenchymal Stem Cells Slow Ageing by Reducing Inflammation

"Inflamm-ageing" describes pro-inflammatory processes that promote ageing. There is evidence that high levels of circulating pro-inflammatory cytokines, such as TNF-α, interleukin-6 (IL-6), and C-reactive protein (CRP), even in "healthy" elderly individuals, are independent predictors of mortality[72].

High levels of TNF-α, IL-6 and CRP correlate with decreased mobility[73], reduced muscle mass and strength[74], and a weaker immune system[75], as well as impaired cardiovascular, pulmonary and neurologic function. Elevated levels of these cytokines thus correlate strongly with early mortality and various causes of death[76]. Increase in systemic inflammation is thought to illustrate a fundamental aspect of the ageing process[77].

It is known that MSCs reduce the expression of pro-inflammatory cytokines, including, TNF-α, interleukin (IL)-1 α, IL-6, and CRP. The paracrine effects of MSCs are produced in response to either secretion of a wide array of individual factors, such as growth factors and cytokines, or via exosomes, small extracellular vesicles that contain peptides, proteins and microRNAs (miRNAs). Factors secreted by MSCs include transforming growth factor (TGF)-α, hepatocyte growth factor (HGF) and interleukins, among many others. Many of these factors interact to produce an immunomodulatory effect[78].

MSCs also affect the immune system through their release of exosomes, which are extracellular vesicles of 40–100 nm size. Ex vivo studies have demonstrated that MSC-derived exosomes reduce secretion of pro-inflammatory cytokines (IL-1ß, TNF-α) and increase production of TGF-ß by PBMCs, but don't affect peripheral blood mononuclear cell proliferation[79]. Administration of MSCs[80] or MSC-derived exosomes[81] reduces the immune response in two mouse models of autoimmune disease, Type 1 diabetes mellitus and uveoretinitis.

These results suggest that MSC-derived Secretome is an effective alternative to Stem Cell Therapy.

[72] Brüünsgaard, Helle, and Bente Klarlund Pedersen. "Age-related inflammatory cytokines and disease." Immunology and Allergy Clinics 23.1 (2003): 15-39.
[73] Ferrucci, Luigi, et al. "Serum IL-6 level and the development of disability in older persons." Journal of the American Geriatrics Society 47.6 (1999): 639-646.
[74] Visser, Marjolein, et al. "Relationship of interleukin-6 and tumor necrosis factor-α with muscle mass and muscle strength in elderly men and women: the Health ABC Study." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 57.5 (2002): M326-M332.
[75] Kanapuru, Bindu, and William B. Ershler. "Inflammation, coagulation, and the pathway to frailty." The American journal of medicine 122.7 (2009): 605-613.
[76] Walston, Jeremy D., et al. "Inflammation and stress-related candidate genes, plasma interleukin-6 levels, and longevity in older adults." Experimental gerontology 44.5 (2009): 350-355.
[77] Gonzalez, Rafael, Dave Woynarowski, and Luis Geffner. "Stem cells targeting inflammation as potential anti-aging strategies and therapies." Cell & Tissue Transplantation & Therapy 2015.7 (2015): 1-8.
[78] Fontaine, Magali J., et al. "Unraveling the mesenchymal stromal cells' paracrine immunomodulatory effects." Transfusion Medicine Reviews 30.1 (2016): 37-43.
[79] Chen, Wancheng, et al. "Immunomodulatory effects of mesenchymal stromal cells-derived exosome." Immunologic research 64.4 (2016): 831-840.
[80] Kota, Daniel J., et al. "TSG-6 produced by hMSCs delays the onset of autoimmune diabetes by suppressing Th1 development and enhancing tolerogenicity." Diabetes 62.6 (2013): 2048-2058.
[81] Shigemoto-Kuroda, Taeko, et al. "MSC-derived extracellular vesicles attenuate immune responses in two autoimmune murine models: type 1 diabetes and uveoretinitis." Stem cell reports 8.5 (2017): 1214-1225.

Results of Anti-Ageing Stem Cell Treatment

Anti-Ageing Stem Cell Therapy is an advanced and novel approach for slowing, and even reversing, the ageing process in humans. Moreover, Anti-Ageing Stem Cell Therapy helps strengthen the remaining cells and encouraging new healthy cell growth.

Patients who have undergone Stem Cell Treatment with Stem Cell Secretome have reported the following improvements:

- Improved appearance of the skin with reduced age spots, even skin tone and fewer lines and wrinkles
- Reduced tiredness
- Improved energy, overall well-being, and vitality
- Relief from aches, pains, and stiffness in joints
- A boost in libido and activity
- Greater muscle strength and reduced flabbiness
- Better organ function
- Better cognition and memory
- Improved mood

Stem Cell Secretome can give humans a cellular "reboot" to keep them healthier for longer.

Ageing and Senescent Cells

Senescent cells are a major factor of ageing. In the young and healthy body, ageing cells kill themselves to make space for new, healthy cells by a process called apoptosis. The lost cells are replaced by new cells from the body's stem cell pool. Ageing cells which fail to kill themselves become senescent cells. At young age, the body's immune system identifies and removes senescent cells from the body. With ageing, the ability of the body's immune system to successfully clear senescent cells is reduced, causing senescent cells to accumulate.

Senescent cells are similar to cancer cells in many aspects, except for forming tumours. But they are harmful to the body, amongst others by causing inflammation, and preventing their replacement by new and healthy cells[82].

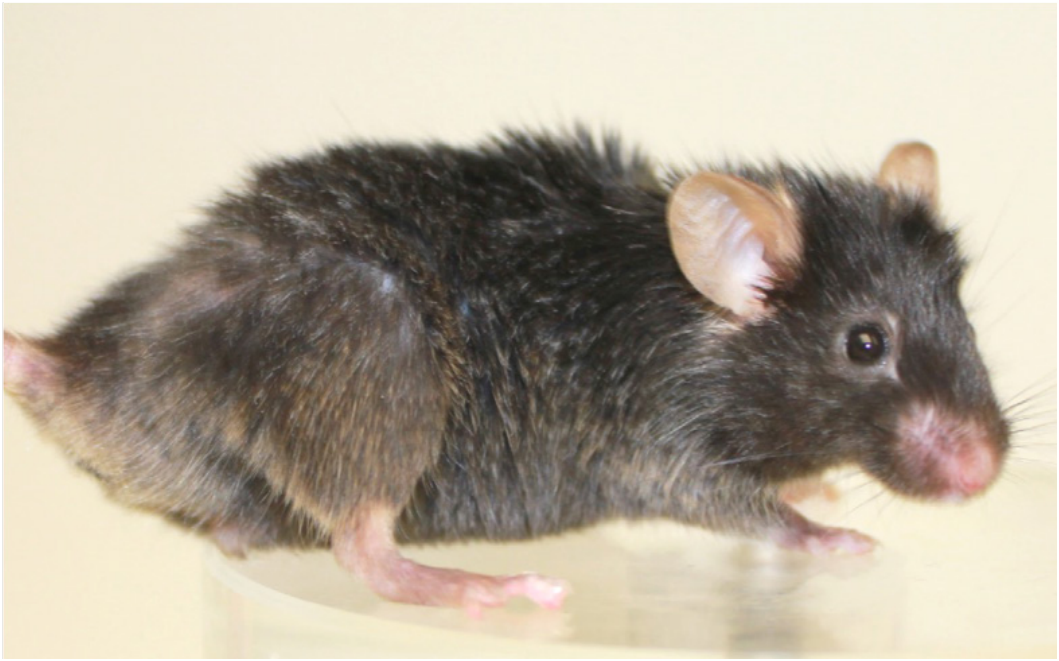
Moreover, senescent cells secrete substances - the so-called senescence associated secretory phenotype (SASP)[83] - which prevent the body's stem cells from repairing damaged tissue, promote age-related diseases and can induce healthy cells to become senescent themselves. This downward spiral turns a rejuvenation process into an ageing process. This way senescent cells negatively affect organ and tissue functions, reducing the pumping function of the heart and the cognitive function of the brain, and make skin wrinkle.

Inflamm-Ageing

In addition to the problems of ageing described above, senescent cells also contribute to another hallmark of ageing: chronic low-grade inflammation, sometimes known as "inflamm-ageing". It is a constant, low-grade level of chronic inflammation, quite different from acute inflammation, which typically subsides after a few days to weeks. Many age-related diseases are linked to inflamm-ageing, making it a significant risk factor to our health as we get older.

[82] Freund, Adam, et al. "Inflammatory networks during cellular senescence: causes and consequences." Trends in molecular medicine 16.5 (2010): 238-246.

[83] Coppé, Jean-Philippe, et al. "The senescence-associated secretory phenotype: the dark side of tumor suppression." Annual Review of Pathological Mechanical Disease 5 (2010): 99-118.



Senolytic Therapies: Senescent Cell Removal Improves Body Function

Removal, i.e. destruction of senescent cells can prevent the negative effects associated with their accumulation in the ageing body. Research shows that significant rejuvenating effects can be achieved by removing just 30% of all senescent cells.

These so-called senolytic therapies have been shown to have significant regenerative effects on cardiovascular function[84, 85] and osteoarthritis,[86] increase the health and lifespan of animals[87] and thus alleviate the symptoms of ageing and for maintaining health as we grow older[88, 89].

Recent research now shows that senescent cells can be removed from the body by small doses of two substances which interfere with the communication between cells. One of those is a so-called tyrosinkinase inhibitor, a medication which, in larger doses and over extended periods of time, is used to treat leukaemia. The other is a substance found naturally in green plants.

This therapeutic approach targets FOXO4 (Forkhead box protein O4) and its influence on the p53 gene, which regulates the cell cycle. Being over-expressed in senescent cells, FOXO4 suppresses apoptosis by interfering with p53. By disrupting the crosstalk between the two, the therapy induces apoptosis in senescent cells. Since this mechanism is found exclusively in apoptotic cells, the senolytic therapy does not have any serious side effects on healthy cells - in contrast to other senolytic drugs such as Navitoclax and similars.

[84] Roos, Carolyn M., et al. "Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice." Aging cell 15.5 (2016): 973-977.

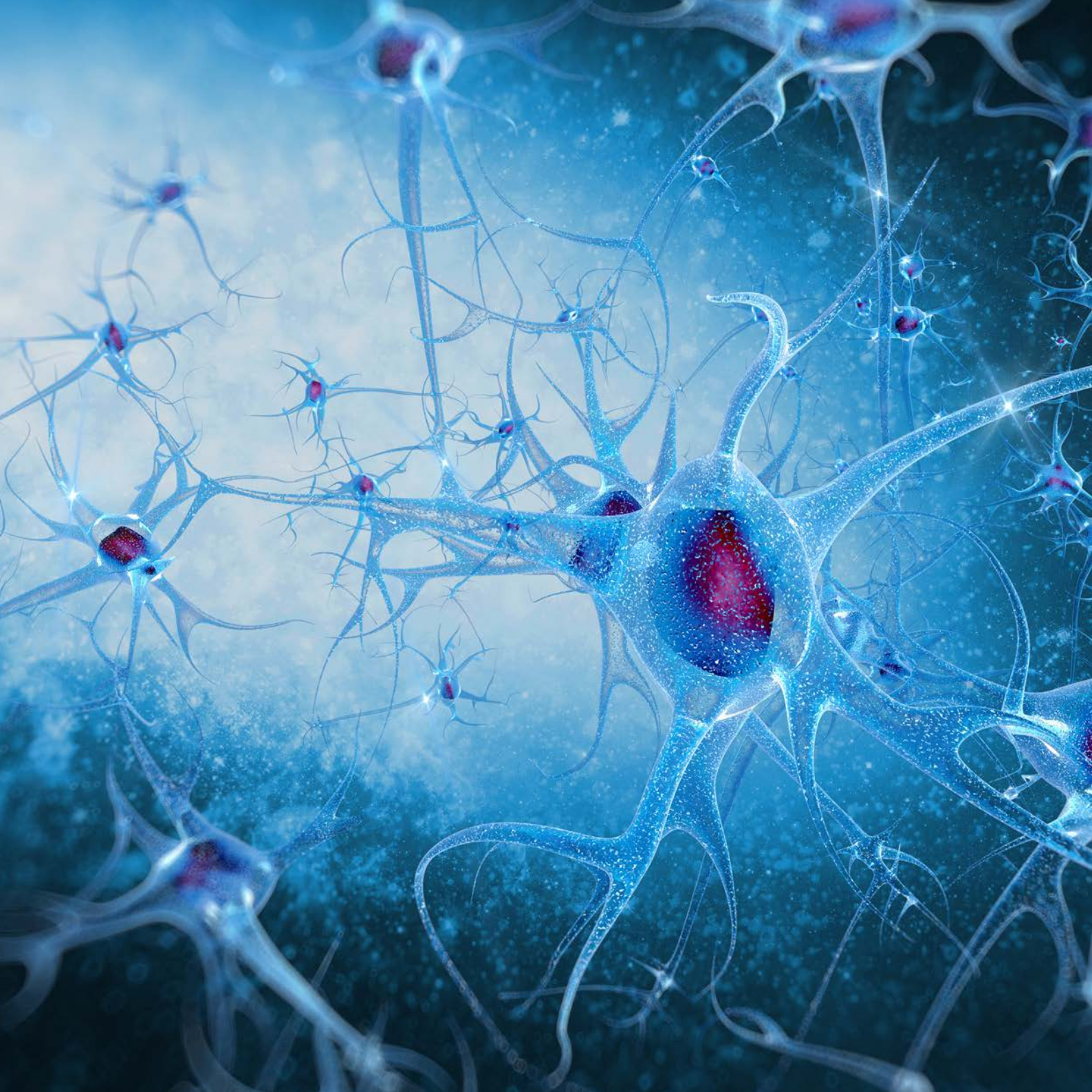
[85] Childs, Bennett G., et al. "Senescent intimal foam cells are deleterious at all stages of atherosclerosis." Science 354.6311 (2016): 472-477.

[86] Xu, Ming, et al. "Transplanted senescent cells induce an osteoarthritis-like condition in mice." The Journals of Gerontology: Series A 72.6 (2017): 780-785.

[87] Baker, Darren J., et al. "Clearance of p16 Ink4a-positive senescent cells delays ageing-associated disorders." Nature 479.7372 (2011): 232.

[88] Tchkonia, Tamara, et al. "Cellular senescence and the senescent secretory phenotype: therapeutic opportunities." The Journal of clinical investigation 123.3 (2013): 966-972.

[89] Zhu, Yi, et al. "The Achilles' heel of senescent cells: from transcriptome to senolytic drugs." Aging cell 14.4 (2015): 644-658.



Antibiotics Eliminate Senescent Cells Associated with Ageing

Latest research from the UK shows that certain antibiotics, prescription medications used to fight bacterial infections, when used appropriately can potentially be turned into life span-enhancing drugs[90].

At only one low-dosage application, Azithromycin was shown to effectively kill and remove senescent cells, derived from human skin and lungs, with an efficiency of 97%. The antibiotic selectively targets senescent cells and forces them to undergo cell death. Moreover, healthy cells thrived in the presence of the drug.

Additionally, it is a relatively mild antibiotic which can extend lifespan in cystic fibrosis patients by several years. Originally it was thought that Azithromycin kills harmful bacteria in cystic fibrosis patients. But the main effect of the antibiotic might be the elimination of inflammatory fibroblasts in the lungs of these patients.

The senolytic effects of Azithromycin is also found in other prescription drugs. These findings imply a potentially alleviation or reversing of tissue dysfunction and slowing the development of many ageing-associated diseases.

[90] Ozsvari, Bela, et al. "Azithromycin and Roxithromycin define a new family of "senolytic" drugs that target senescent human fibroblasts." Aging (Albany NY) 10.11 (2018): 3294.

Topical Application of Prescription Drugs and Stem Cell Products for Beautiful Skin and Hair

With ageing changes take place in skin, which make it lose its youthful tone and complexion. Changes in skin of the scalp are the cause for hair loss, both in men and women.

Since most of the ageing-related changes happen within 5 mm from the surface of the skin, topically applied substances can be effective to restore a more youthful appearance. This is what makes the beauty industry worth an astounding $382 billion globally.

Many cosmetics, however, are ineffective, mainly for two reasons: They do not contain the powerful drugs which require a prescription from a medical doctor or which need to be produced in a certified stem-cell laboratory; and they do not use effective carrier substances which can deliver the active ingredient from the surface into the deeper layers of the skin.

At ANOVA Institute for Regenerative Medicine we design and produce tailor-made solutions for your specific skin and hair problems.

Together with our pharmacologists ANOVA Institute for Regenerative Medicine has developed a unique solution for hair loss (alopecia) in men, which goes to the root of the hair problem with a novel carrier system and effective ingredient to stop alopecia.

For better skin, we have developed optimised carrier systems to carry active pharmaceutical components into the skin to improve skin tone, elasticity and surface structure to reduce age-related wrinkling and heterogeneity.

Talk to our clinical experts and have a powerful tailor-made topical remedy developed for your specific skin and hair problem.

ANOVA Institute for Regenerative Medicine
German Stem Cell Engineering - Designed for Results

Next Generation Medicine

ANOVA Institute for Regenerative Medicine is a German clinic for translational regenerative and cellular medicine. ANOVA provides Stem Cell Treatments based on current stem cell research and state-of-the-art technology.

At ANOVA, we endeavour to improve the health and well-being of those we serve with a commitment to excellence. Our goal is to make Stem Cell Treatments available to patients now - in the true sense of translational and individualised medicine.

Knowledge on Stem Cell Treatments is developing rapidly. At ANOVA each patient's Stem Cell Treatment is therefore based on an analysis of the latest scientific facts, which we make available to the patient. This way, we stay at the forefront of translational medicine and within the bounds of science.

Who We Are

ANOVA Institute for Regenerative Medicine is the first Stem Cell Treatment centre in Europe which is fully certified under German and European law. ANOVA operates under the supervision of the Hessian Government and the Paul-Ehrlich-Institut.

Together with a state-of-the-art diagnostic centre providing imaging, laboratory and genetic testing, and a small private hospital with modern facilities, it provides personalised medical services at the highest level.

ANOVA is conveniently located between Frankfurt and Offenbach, 15 minutes from Frankfurt airport.

Why Stem Cells?

Mesenchymal Stem Cells (MSCs) are adult stem cells characterised by their self-renewal ability and multi-potency. Besides replacing lost and damaged cells, they respond specifically to tissues and organ damage, down-regulate inflammation, suppress apoptosis (cell suicide), improve blood supply, and activate organ-specific stem cells for repair.

At ANOVA we manufacture tissue preparations derived from MSCs obtained from adipose tissue and ATMPs based on bone marrow-derived stem cells - powerful regenerative agents for treating many disease processes. The manufacturing process is strictly quality controlled by German and European law.

Our Stem Cell Products

The Stem Cell Secretome

Recent scientific research has revealed that the healing power of stem cells is mainly derived from secreted bioactive compounds, such as micro-RNA, growth factors, extracellular vesicles and cytokines - summarily called the Stem Cell Secretome.

These paracrine factors function as messengers between the cells. Through them, tissue and organ repair and regeneration, anti-inflammatory and anti-ageing properties are effected.

Bone Marrow Concentrate

Bone Marrow Stem Cells are abundant available and easily accessible. They have been shown to be of particular benefit in degenerative joint disease, sports injuries, and a variety of neurological disorders. ATMPs based on BMC are immediately available for treatment, as the production process can be completed within a few hours.

Your Personalised Therapy

At ANOVA, Bone Marrow Stem Cells (BMC), Mesenchymal Stem Cell Secretome (MSCS), platelet rich plasma, detox infusions, hormonal optimisation, biochemical and genetic analysis and whole-body imaging are part of the spectrum we use to provide the best in individualised regenerative medicine.

Diagnostic Work-Up at ANOVA:

- In-depth medical history
- General physical examination
- Whole-body MRI
- Advanced imaging: Coronary CT, virtual endoscopy, etc.
- Personalised laboratory diagnostics
- Genetic screening

Personalised Medicine Programmes at ANOVA

- Personalised rehabilitation programmes
- Dietary optimisation
- Hormone optimisation
- Metabolic and body composition optimisation

Conditions benefiting from ANOVA's Stem Cell Treatments

- Sports injuries
- Degenerative joint disease – osteoarthritis (OA)
- Inflammatory and auto-immune disorders (e.g. rheumatoid, arthritis, multiple sclerosis)
- Ischaemic neurological disorders (e.g. stroke)
- Neuro-degenerative disorders (e.g. Alzheimer's disease, ALS)
- Erectile Dysfunction
- Diabetes Mellitus
- Anti-Ageing

Overview:

Stem cells hold these major beneficial properties:

- Reduce tissue and cell injury
- Protect tissue from degeneration
- Promote tissue and organ regeneration
- Enhance tissue and wound healing
- Down-regulate inflammation
- Slow down the ageing process

At ANOVA each treatment is tailored to the patient's specific needs in 3 steps:

1. Diagnostic work-up tailored to the patient's specific condition.
2. Analysis of scientific data supporting the effectiveness of stem cells for the patient's condition.
3. Implementation of an individualised treatment programme.

ANOVA Institute for Regenerative Medicine - the first to introduce the Stem Cell 2.0 Therapy - Mesenchymal Stem Cell Secretome.

Meet the dedicated team of ANOVA Institute for Regenerative Medicine:
Expert medical professionals and scientists, ready to provide you with the high quality medical care you deserve.

Michael K. Stehling

MD, PhD
Professor of Radiology,
fmr. Clinical Fellow
Harvard Medical School, Boston, USA
fmr. Associate Professor of Radiology
at Boston University, USA.

Johannes Atta

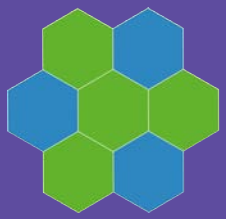
MD
Professor of Haematology,
Specialist in Internal Medicine,
Haematology and Clinical Oncology,
Medical Quality Management.

Contact

ANOVA
Institute for Regenerative Medicine GmbH

Strahlenberger Straße 110
63067 Frankfurt am Main
Offenbach, Germany

Phone: +49 (0) 69 50 50 00 944
Email: info@anova-irm.com
Internet: www.anova-irm.com



ANOVA

Institute for Regenerative Medicine