Treating Osteoarthritis

Joint Preservation with Cellular Therapies

ANOVA

Institute for Regenerative Medicine

Dear reader,

Osteoarthritis (OA) – or degenerative joint disease - is a common ailment of joints which affects hundreds of millions of people worldwide. The disease leads to a significant reduction in quality of life of those affected. Pain and functional limitations often cause secondary health and psycho-social problems.

Contrary to cancer, there are no established prevention and early detection programs for osteoarthritis. At best they slow down the progression of the disease and/or relieve pain. In advanced stages joint replacement with an endo-prosthesis often remains the only option.

Despite this, currently there are no prevention and early detection programmes for osteoarthritis, although scientific studies have shown that both could be established using Magnetic Resonance Imaging (MRI).

In this brochure, we provide an overview of modern approaches to early detection and treatment of osteoarthritis with the aim of preventing the disease and regenerating affected joints.

We introduce you to the latest therapeutic approaches that combine the possibilities of cellular medicine under consideration of metabolic and functional aspects.

We hope to welcome you soon in our clinic.

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

Osteoarthritis – A Scourge of Advanced Age

Osteoarthritis (OA) - the wear and tear of joints - affects everybody sooner or later. Arthritic joint changes are detectable in 80% of 65-year-olds; 60% suffer from symptoms[1].

Osteoarthritis is caused by degenerative changes of the articular cartilage and underlying bone, two of the major components of joints. Inflammation of the synovial membrane, the inner lining of the joint, also play an important role during the degeneration process[2, 3].

The main symptoms are joint pain, limited motor function and stiffness. Osteoarthritis often affects the joints of hands, feet, spine and knees. The main risk factors are genetic, but obesity, joint injuries, lack of exercise and imbalanced sex hormones also play a role.

[1] Neogi, Tuhina. "The epidemiology and impact of pain in osteoarthritis." Osteoarthritis and Cartilage 21.9 (2013): 1145-1153.
[2] Goldring, Mary B., and Steven R. Goldring. "Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis." Annals of the New York Academy of Sciences 1192.1 (2010): 230-237.
[3] Ilshiguro, Naoki, Toshihisa Kojima, and A. Robin Poole. "Mechanism of cartilage destruction in osteoarthritis." Nagoya journal of medical science 65.3-4 (2002): 73-84.

Established Therapies for OA - Ineffective and Often Harmful

Established therapies for osteoarthritis are aimed at reducing pain, and ideally at slowing down degenerative changes.

Oral anti-inflammatory and pain medications such as acetaminophen, non-steroidal anti-inflammatory drugs, and weak opioid analogues can relieve symptoms in the early stages of osteoarthritis[4].

Whilst classic anti-inflammatory drugs (NSAIDs - non-steroidal anti-inflammatory drugs), such as ibuprofen, cause damage to the stomach and kidneys, the so-called COX2 inhibitors have since been largely withdrawn from the market because of an increased risk of heart attack and stroke.

Injection Therapies are commonly used in patients with unsatisfactory response to the above mentioned oral therapies. The intra-articular injection of corticosteroids is still widely used today[5, 6]. However, their effect usually does not last longer than 4 weeks[7].

Although the injection of cortisone preparations into the inflamed joints results in rapid pain relief, it accelerates joint wear by damaging the cartilage cells, which are essential for the maintenance of articular cartilage.

Synthetic hyaluronic acid (HA), whose natural form is part of the synovial fluid, has been used for decades to aid the viscosity of the joint and suppress inflammation. While previous meta-analyses considered HA superior to cortisone injections, this effect could not be addressed in a recent large-scale meta-analysis[8].

Therefore, while medication may help relief the symptoms, they may cause severe side effects that can still heavily impact the quality of life of the patients.

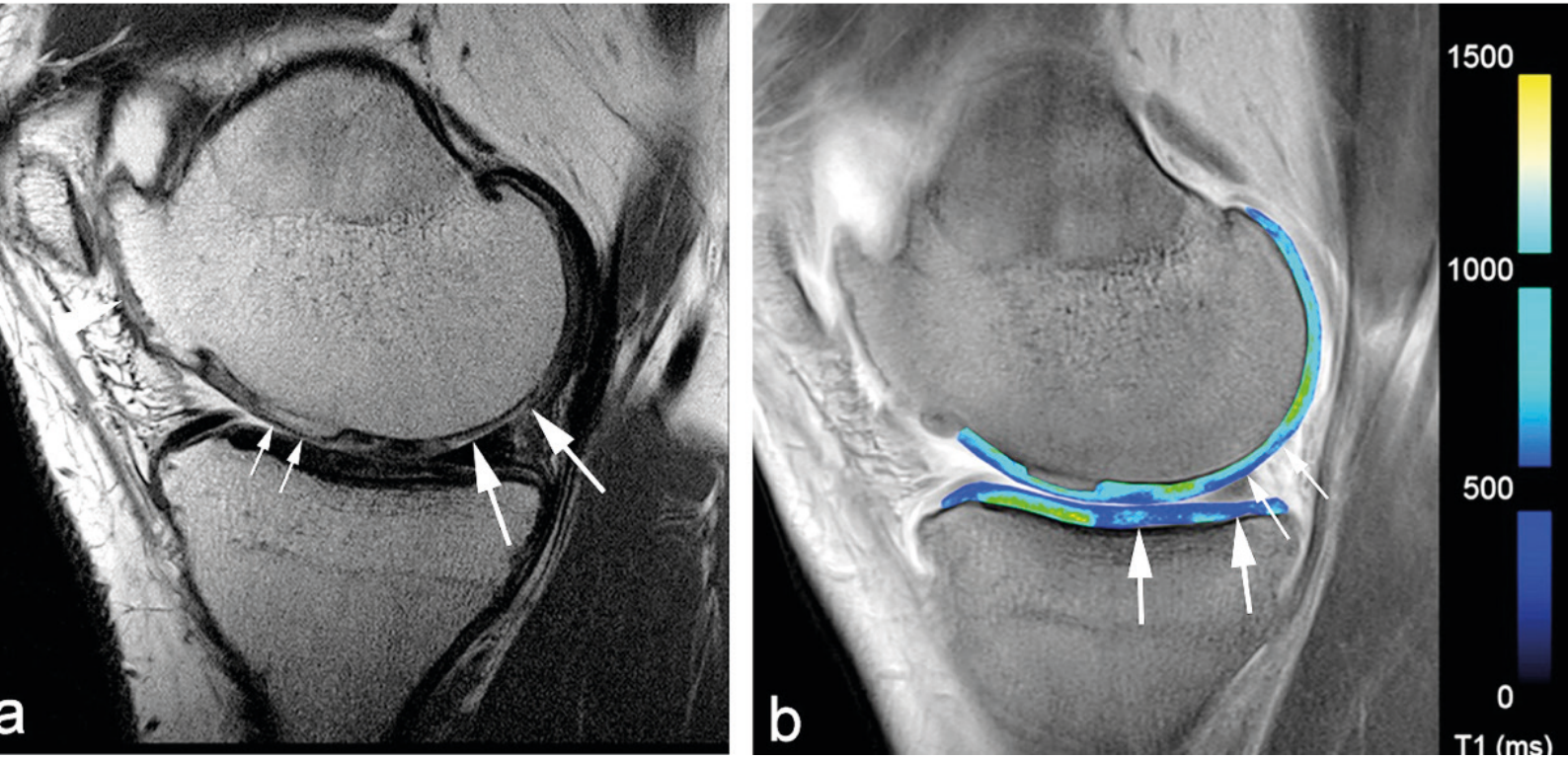
[4] Jordan, K. M., et al. "EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT)." Annals of the rheumatic diseases 62.12 (2003): 1145-1155.

[5] Hameed, Farah, and Joseph Ihm. "Injectable medications for osteoarthritis." PM&R 4.5 (2012): S75-S81.

[6] Cheng, Olivia T., et al. "Evidence-based knee injections for the management of arthritis." Pain medicine 13.6 (2012): 740-753.

[7] Bannuru, Raveendhara R., et al. "Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis." Arthritis Care & Research 61.12 (2009): 1704-1711.

[8] Rutjes, Anne WS, et al. "Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis." Annals of internal medicine 157.3 (2012): 180-191.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Early Detection of Joint Changes May Avoid Osteoarthritis

While in cancers, the concept of avoidance by early detection of benign cancer precursors has long been established, e.g. colon polyps or "carcinoma in situ" of the breast, such prevention concepts do not exist for osteoarthritis.

In medical expert circles, however, the concept of "pre-arthritis" has recently been scientifically discussed. With the help of modern imaging techniques, it is possible to visualize early onset structural changes in articular cartilage and subchondral bone structure that indicate the onset of osteoarthritis. Magnetic Resonance Imaging (MRI) and Optical Coherence Tomography (OCT) play an important role in this, with OCT instruments being introduced into the joint[9].

If detected early on, disease progression can be controlled: relieving the joints, improving biomechanics, sports, hormone replacement and regenerative therapies with cytokines and stem cells can slow down OA.

Arthro-MRI Shows the Cause of Joint Pain

In today's modern medicine, MRI of the joints - the Arthro-MRI - can detect early signs of deterioration of articular cartilage and bone, ligaments and menisci as well as inflammatory changes of the joint cavity. Through the use of contrast agents, joint pain can be precisely assigned to specific structures, because not every structural change (such as the tear of a meniscus) inevitably leads to pain. Only if the structural change on special MRI 3D sequences is associated with an uptake of the contrast agent, the cause of the complaints can be confirmed.

OA Detection Through Blood Tests? Possible in the Near Future

In the near future it may even be possible to detect early changes which indicate osteoarthritis with a simple blood test[10]. Until then, clinical investigations and imaging studies, most notably arthro-MRI, remain the best way to detect early stage osteoarthritis.

[10] Braun, Hillary J., and Garry E. Gold. "Diagnosis of osteoarthritis: imaging." Bone 51.2 (2012): 278-288.

[11] Ahmed, Usman, et al. "Protein oxidation, nitration and glycation biomarkers for early-stage diagnosis of osteoarthritis of the knee and typing and progression of arthritic disease." Arthritis research & therapy 18.1 (2016): 250.

The Connection between Hormone Imbalance and Osteoarthritis

- University of Gothenburg:
  Optimised estrogen levels reduce the inflammation and progressive destruction of joints.
- Oxford University:
  In post-menopausal women with artificial knee or hip joints, the need for a corrective second operation is reduced by 40%, when they receive hormone replacement therapy.
- Wake Forrest University:
  Estrogens have a direct positive effect on the articular cartilage in adults. They increase the production of the growth factor IGFBP-2, which stimulates cartilage cells to produce proteoglycans in articular cartilage.
- Monash University:
  Low sex hormone levels correlate with increased inflammation, swelling, and structural changes in arthritic joints.
- Monash University:
  Testosterone protects against osteoarthritis. Overweight men with higher testosterone levels have a lower risk of needing a knee or hip joint replacement.
- Harvard Medical School:
  Testosterone replacement in men who have low levels of testosterone due to the chronic use of painkillers reduces pain perception, increases the ratio of muscle mass to body fat, libido, and quality of life.

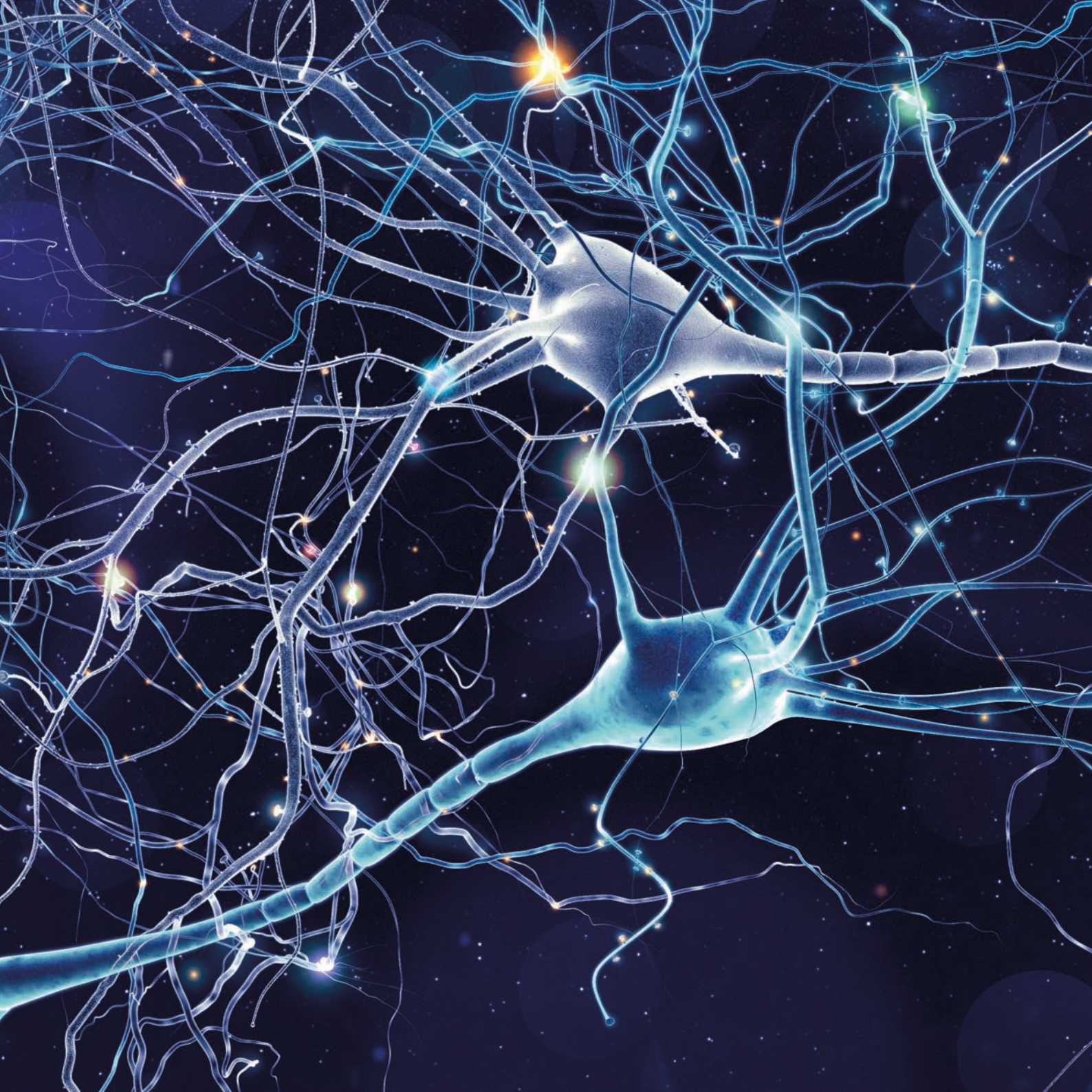
Hormonal Optimisation: An Important Component of OA Treatment

Estrogen and testosterone are the most important sex hormones in both women and men. They are essential for the general well-being. Hormones play an important role in maintaining healthy bones and muscles, the immune system, tissue regeneration and most other functions of a healthy body. New research shows that hormones also play an essential role in the development of degenerative joint disease.

At ANOVA Institute for Regenerative Medicine we routinely check the following hormone levels, amongst others, to optimise patients' health, healing, and slow down ageing:

- Thyroid hormones
- TSH
- DHEA
- Pregnenolone
- Estrogen
- Progesterone
- Testosterone
- Melatonin
- Cortisol
- TBG (testosterone binding globuline)

For patients with degenerative joint disease and chronic pain, it is very likely that abnormalities in at least some of these hormone levels will be found - and can be brought back to normal.



Cellular Therapies for OA – Mesenchymal Stem Cells

Current therapies of osteoarthritis are mostly targeting symptoms. None of them, however, can directly modify the pathophysiological processes of OA; nor can they prevent the progress of the disease.

Stem Cell Therapies, on the other hand, have yielded impressive results in regenerating damaged tissues and the underlying ageing and immunologically-related processes of osteoarthritis.

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. 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. MSCs are currently seen as a useful treatment for dozens of pathological conditions and disorders.

The anti-inflammatory, restorative and immunomodulatory qualities of stem cells have been shown to be effective for the treatment of a wide range of pathological conditions, including cardiovascular[11] and neurologic diseases, such as stroke[12], spinal cord injuries[13], and Parkinson's disease[14]; autoimmune diseases such as multiple sclerosis[15] and systemic lupus erythematosus[16] as well as the healing of wounds[17] and the repair of cartilage defects[18] in osteoarthritis.

[11] 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.

[12] 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.

[13] 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.

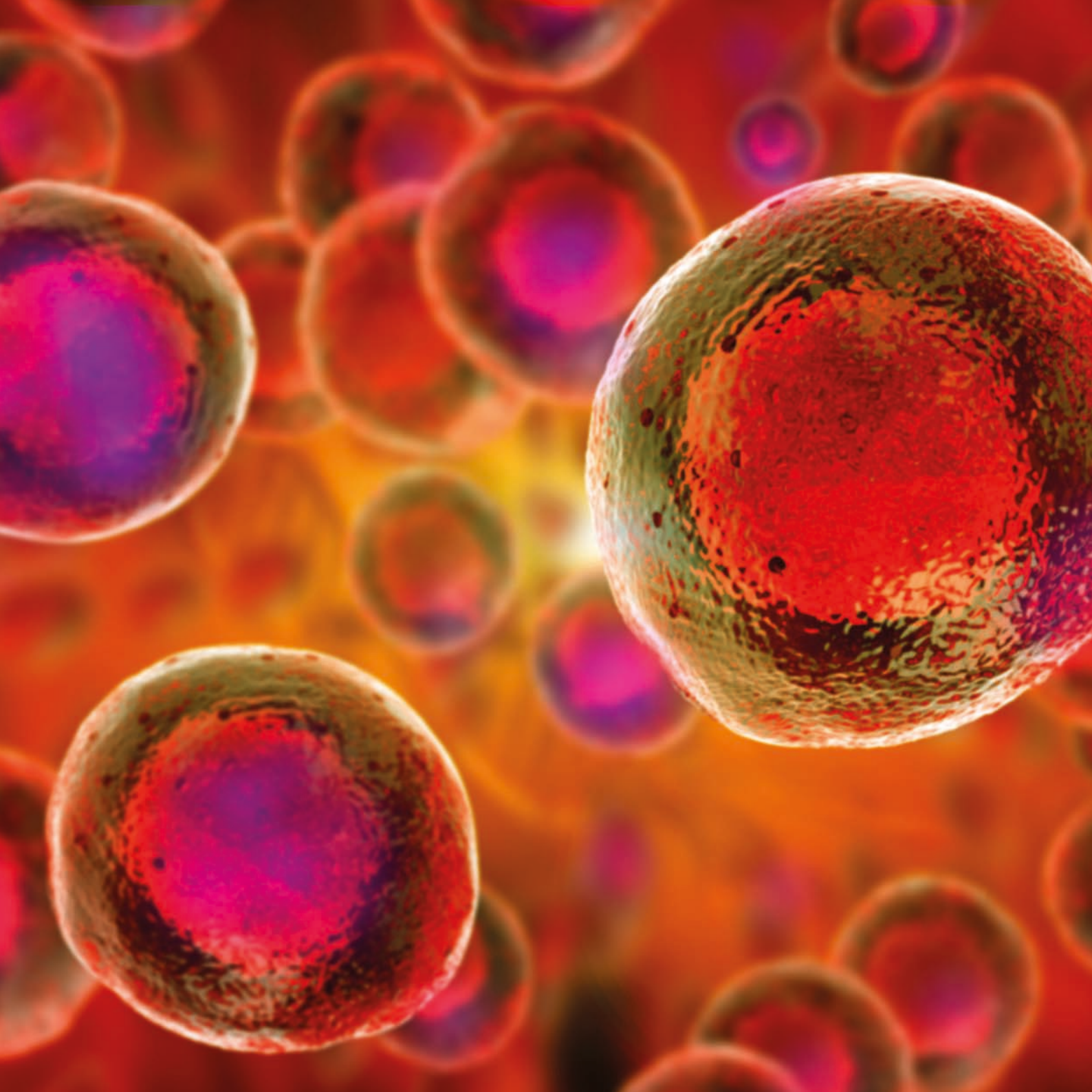
[14] Venkataramana, Neelam K., et al. "Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease." Translational Research 155.2 (2010): 62-70.

[15] 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.

[16] 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.

[17] 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.

[18] 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.



Cellular Therapies for OA – Stem Cell Secretome

Recent evidence-based scientific research[19] has shown that Stem Cell-based Therapies are able to effectively modulate the immune responses of OA, regenerate lost nerve supply, differentiate into chondrocytes (the cells that produce cartilage), etc., and offer long lasting effects for treating OA, as compared to standard medications (like nonsteroidal anti-inflammatory drugs) which only temporarily mask the symptoms.

With the next generation of Stem Cell-based Therapies, the ANOVA Stem Cell Secretome Therapy, in combination with conventional therapeutic measures, we offer a novel regenerative approach to treating osteoarthritis.

Stem Cell Secretome is the sum of all healing components of stem cells. ANOVA's team has implemented a scientific process that elegantly and efficiently harvests and concentrates the therapeutic components produced by stem cells that are responsible for the stem cells' healing power. The aim of this process is to induce the production of the specific regenerative substances that stem cells are secreting, to concentrate and utilise them for the treatment of the condition that the patient is suffering from.

Stem Cell Secretome Therapy can effectively be used in combination therapy with Bone Marrow Concentrate (BMC). BMC is a source for Mesenchymal Stem Cells (MSCs). It contains many important growth and regenerative factors, in addition to Mesenchymal Stem Cells. The procedure is relatively simple and minimally invasive, therefore it has been a favorite source for Stem Cell-based Therapies in the previous decades. Many groups rely on BMC as their main Stem Cell Treatment, sometimes with exaggerated claims. However, BMC has demonstrated impressive results for effective treatment of numerous diseases, among them being osteoarthritis[20]. Especially in combination with Stem Cell Secretome, BMC Treatment can unfold its full potential.

[19] Khatab, S., et al. "Mesenchymal stem cell secretome reduces pain and prevents cartilage damage in a murine osteoarthritis model." European cells & materials 36 (2018): 218-230.

[20] Themistocleous, George S., et al. "Effectiveness of a single intra-articular bone marrow aspirate concentrate (BMAC) injection in patients with grade 3 and 4 knee osteoarthritis." Heliyon 4.10 (2018): e00871.

Platelet Rich Plasma (PRP) for the Treatment of OA

Many famous athletes have received PRP for various orthopaedic problems, such as sprained knees and chronic tendon injuries. These types of injury are typically treated with medications, physical therapy, or surgery. But some athletes have credited PRP with their ability to return more quickly to competition.

Platelet Rich Plasma (PRP), also referred to as autologous conditioned plasma, is a biological therapeutic consisting of a concentrate of platelet and plasma proteins containing growth factors and other cytokines, free in solution or in microvesicles[21].

These constituents of PRP can accelerate repair processes in tissues and organs. The regenerative properties of PRP have been studied in various medical conditions, such as chronic tendinitis[22], OA[23, 24], as well as in oral[25] and plastic surgery[26].

The numerous growth factors contained in PRP have been shown to induce repair and replacement of damaged cartilage by stimulating cartilage matrix synthesis and counteract the effects of catabolic cytokines, such as interleukin-1 and tumor necrosis factor-α. These growth factors have been found to possess synergistic effects on cartilage matrix synthesis[27] and are known to induce further growth factor protein production by neighboring articular chondrocytes[28].

[21] Laver, Lior, et al. "PRP for degenerative cartilage disease: a systematic review of clinical studies." Cartilage 8.4 (2017): 341-364.

[22] Mishra, Allan, James Woodall Jr, and Amy Vieira. "Treatment of tendon and muscle using platelet-rich plasma." Clinics in sports medicine 28.1 (2009): 113-125.

[23] Laver, Lior, et al. "PRP for degenerative cartilage disease: a systematic review of clinical studies." Cartilage 8.4 (2017): 341-364.

[24] Andia, Isabel, Mikel Sánchez, and Nicola Maffulli. "Joint pathology and platelet-rich plasma therapies." Expert opinion on biological therapy 12.1 (2012): 7-22.

[25] Esposito, Marco, et al. "Effectiveness of sinus lift procedures for dental implant rehabilitation: a Cochrane systematic." Eur J Oral Implantol 3.1 (2010): 7-26.

[26] Por, Yong-Chen, et al. "Use of tissue sealants in face-lifts: a metaanalysis." Aesthetic plastic surgery 33.3 (2009): 336-339.

[27] Abd-Elsayed, Alaa. "Stem cells for the treatment of knee osteoarthritis: a comprehensive review." Pain physician 21 (2018): 229-241.

[28] Bendinelli, Paola, et al. "Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: Mechanisms of NF-kB inhibition via HGF." Journal of cellular physiology 225.3 (2010): 757-766.

The Advantages of Platelet Rich Plasma

PRP is a relatively simple precursor of Stem Cell-based Therapies with several advantages which have been shown in a long track record of successful clinical trials.

- Platelet Rich Plasma Injections consist of concentrated platelets from the patient's own blood. Injections are usually directly into damaged cartilage and tendons. This can reduce pain and help aid in the natural healing process.
- PRP can accelerate the process of rebuilding tissues in common tendon injuries, such as tennis elbow or Achilles tendinitis. It can also be utilised to facilitate healing of cartilage due to osteoarthritis or other damages.
- PRP Injections are sometimes performed in a series of treatments, but often patients experience life-changing results already after the first injection.

Common orthopaedic applications include:

- Osteoarthritis of the knee, hip, spine and shoulder
- Tennis elbow (epicondylitis)
- ACL injuries
- Achilles tendinitis
- Bone fracture healing
- Chronic inflammations of tendons and cartilage throughout the body

Role of Exercise in OA Management

Exercise may offer additional benefits to improving or modifying arthritis. As Dr. Steven Blair, Exercise Epidemiologist and Director of Epidemiology at the Cooper Institute for Aerobics Research in Dallas TX notes:

"Skeletal muscle is the largest organ in the body and is intricately tied with protein turnover and synthesis and many other metabolic and biochemical functions. Activating skeletal muscle has many important health benefits we are only beginning to understand."

Physical activity is known to play a vital role in the management of arthritis. Regular physical exercise will keep the muscles surrounding affected joints strong, prevent or decrease bone loss and may even decrease joint swelling. Regular activity can further reduce stiffness and pain.

The goals of an exercise programme for individuals with arthritis are to preserve range of motion and flexibility around affected joints, increase muscle strength and endurance, and increase physical conditioning to improve mood and decrease health risks associated with an inactive lifestyle.

At ANOVA Institute for Regenerative Medicine, we work together with local physiotherapists and with your personal physiotherapist at home, to ensure you receive the therapy programme that is most effective for you.

ANOVA's Comprehensive Treatment Programme for Osteoarthritis:

Stem Cell Therapy is rapidly developing into an effective and safe treatment for OA. To obtain best results, Stem Cell Therapy needs to be integrated into a comprehensive treatment program, which addresses all aspects of the condition.

At ANOVA, our physicians work together with specialists to address all of these issues to ensure optimal outcomes:

- Comprehensive diagnostics, including imaging and bloodwork
- Hormone optimisation
- Choice of natural food supplements to support healing processes
- Individual sports, exercise and physiotherapy programmes
- Stem Cell Treatments best suited for your condition:
  - ◊ Mesenchymal Stem Cells
  - ◊ Stem Cell Secretome
  - ◊ Platelet Rich Plasma
  - ◊ or a combination thereof

Our medical professionals, a team of dedicated physicians, patient care managers and scientists, are ready to provide you with the high quality medical care that you deserve.

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.

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