SPINAL CORD INJURY:

FROM WHEELCHAIR TO WALKING WITH STEM CELLS AND ROBOTIC EXOSKELETONS

ANOVA IRM
Stem Cell Center

Dear Reader,

Spinal cord injury is a devastating, life changing injury, often afflicting young people. In the past there were few treatment options.

Now there is new hope for patients with spinal cord injury. The combination of stem-cell based neuro-regeneration with neuro-functional robotic exoskeleton training offers realistic hope to get out of the wheelchair and walk again. In Germany we made this possible by a unique collaboration between ANOVA Institute for Regenerative Medicine in Offenbach and Cyberdyne, a Japanese company in Bochum.

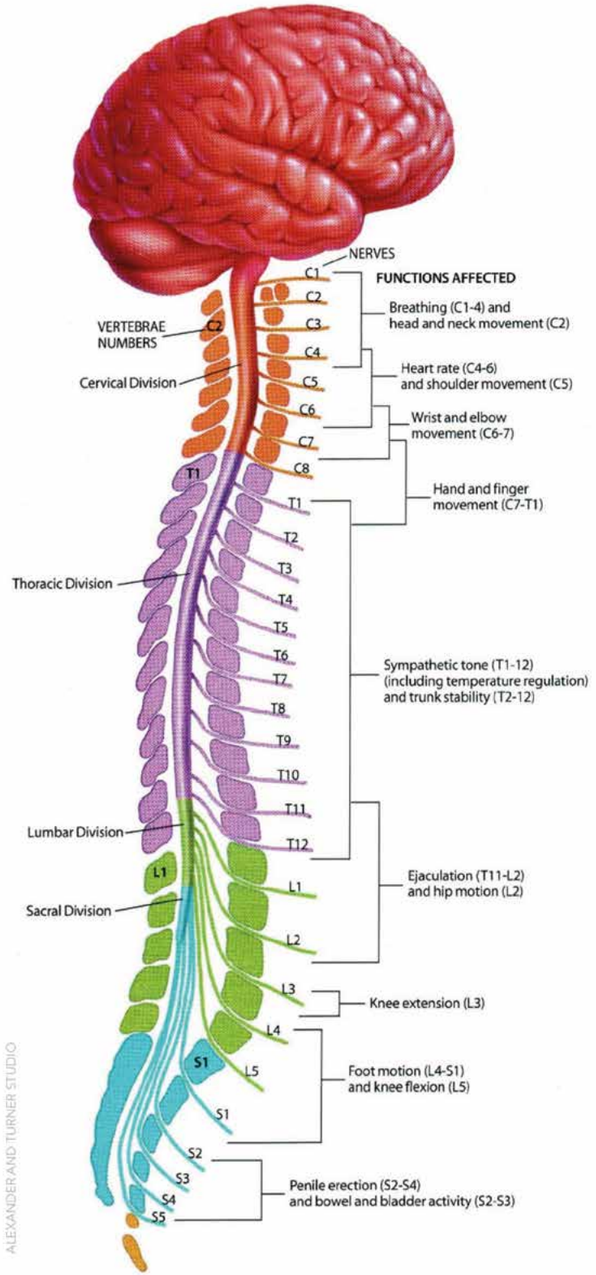
Whilst ANOVA is the first institution in Europe to have obtained an official license for producing and treating patients with mesenchymal and bone marrow stem cells, Cyberdyne has developed the HAL exoskeleton for neuro-functional feedback training.

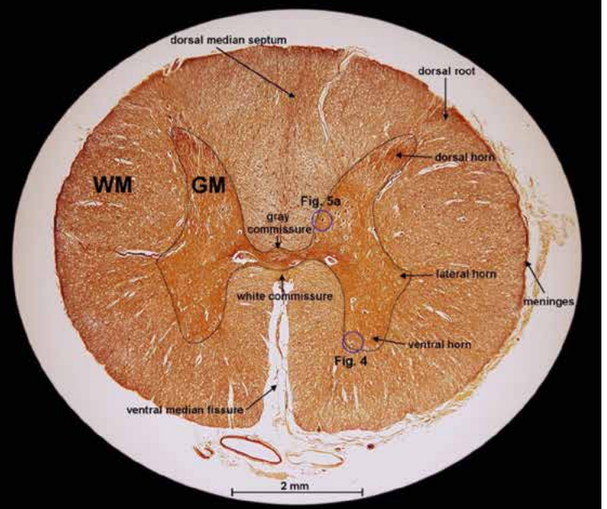
At **ANOVA IRM** we have successfully combined these two ground-breaking treatments to provide paralysed patients with a real chance to get out of the wheelchair and walk again – taking neuro-rehabilitation into the 21st century. If you are suffering from spinal cord injury, talk to us to find out about the first officially approved stem cell therapy for SCI in Europe.

We hope to welcome you soon in our clinic.

Prof. Dr. mult. Michael K. Stehling

ANOVA Institute for Regenerative Medicine





The Spinal Cord: Structure and Function

The Spinal Cord (SC) connects the brain with the peripheral nerves. It runs inside the bony canal of the spine, suspended in the cerebro-spinal fluid (CSF). Whilst measuring only 8 - 12 mm in diameter, the SC contains billions of nerve cells and nerve fibres (axons), which conduct motor signals from the brain to the muscles and sensory signals from the peripheral nerves back to the brain.

The spin cord's neuroanatomy is immensely complex and can best be compared to a computer chip: its elements are tiny, of the order of micro-meters. Assessment of damage to the SC is thus mainly performed by functional tests, with imaging such as MRI only playing an auxiliary role because of its limited resolution.

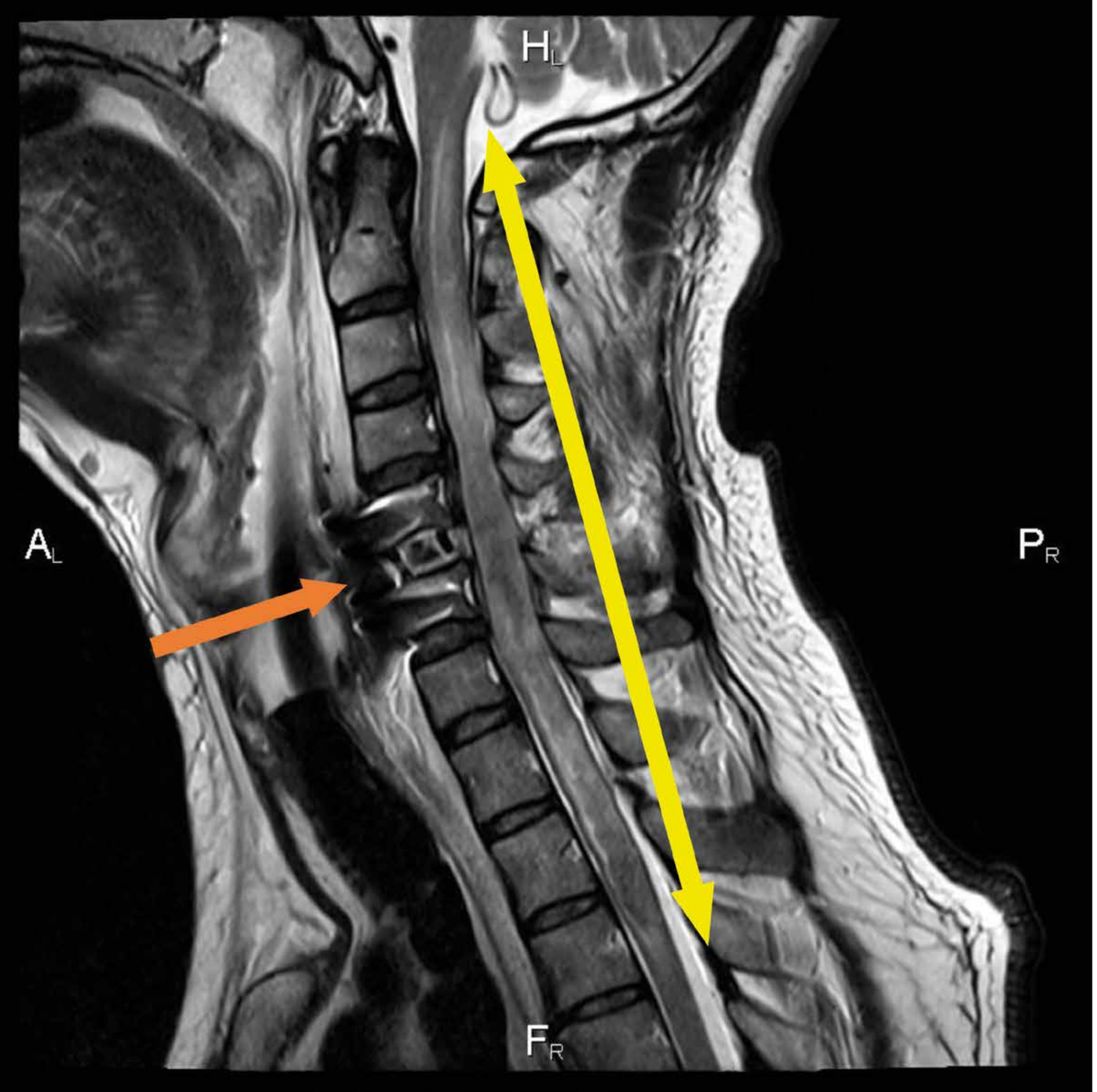
Spinal Cord Injury: Causes and Consequences

Spinal cord injury[1] (SCI) is a devastating condition. It affects millions of people worldwide, mainly younger males. Most cases of SCI are caused by physical trauma from motor vehicle accidents (MVA), gunshot wounds, falls and sports injuries. Fewer are non-traumatic. Approx. 50% of SCI occur at the cervical spine.

Symptoms of SCI include the loss of voluntary motor control, muscle spasticity, loss of sensation, pain and loss of autonomic functions such as bowel or bladder control and erectile dysfunction. Patients with SCI often lose their ability to walk, needing wheelchairs, and often require lifelong care.

Damage to the spinal cord occurs not only at the instant of the injury, but also later, up to weeks after the injury, caused by ischaemia (lack of blood supply), inflammation, swelling, cell suicide, and neurotransmitter imbalances.

[1] https://en.wikipedia.org/wiki/Spinal_cord_injury



Because of the complexity of the injury mechanism, early hospital treatment is very important, with the main goal to ensure adequate spinal cord perfusion. This can be achieved by decompression surgery and maintaining adequate blood pressure and oxygen supply.

Spinal cord injuries are classified into “complete” and “incomplete”. In complete SCI all functions below the injured area are lost, whether or not the spinal cord is severed. An “incomplete” spinal cord injury involves preservation of motor or sensory function below the level of injury in the spinal cord.

The figure on the left shows a patient with SCI after a fracture at level C5/6. The primary damage is at this level (orange arrow). There is, however, secondary damage to the spinal cord from level C1 down to Th3 (yellow arrow) caused by compression of the cord from swelling (oedema) which in turn caused cessation of the blood supply to the spinal cord. This is due to the fact that the swollen spinal cord could not expand in narrow spinal canal. Surgical widening of the spinal canal by removal of the posterior bony elements (laminectomy) was not performed in this patient early enough to prevent the secondary damage.

Are Current Concepts of Neuro-Rehabilitation Outdated?

In the past the initial ASIA score[2], as determined 72 hours after the SCI, was thought to predict how much functional recovery a SCI patient could achieve. In patients with "complete" SCI (ASIA A), i.e. no remaining motor function or sensation below the level of injury, generally very little recovery potential was prognosticated.

It was also assumed that most motor recovery occurs in the subacute phase of SCI, 6 - 12 months after the injury. Little further functional improvement was considered possible during the chronic stage of SCI.

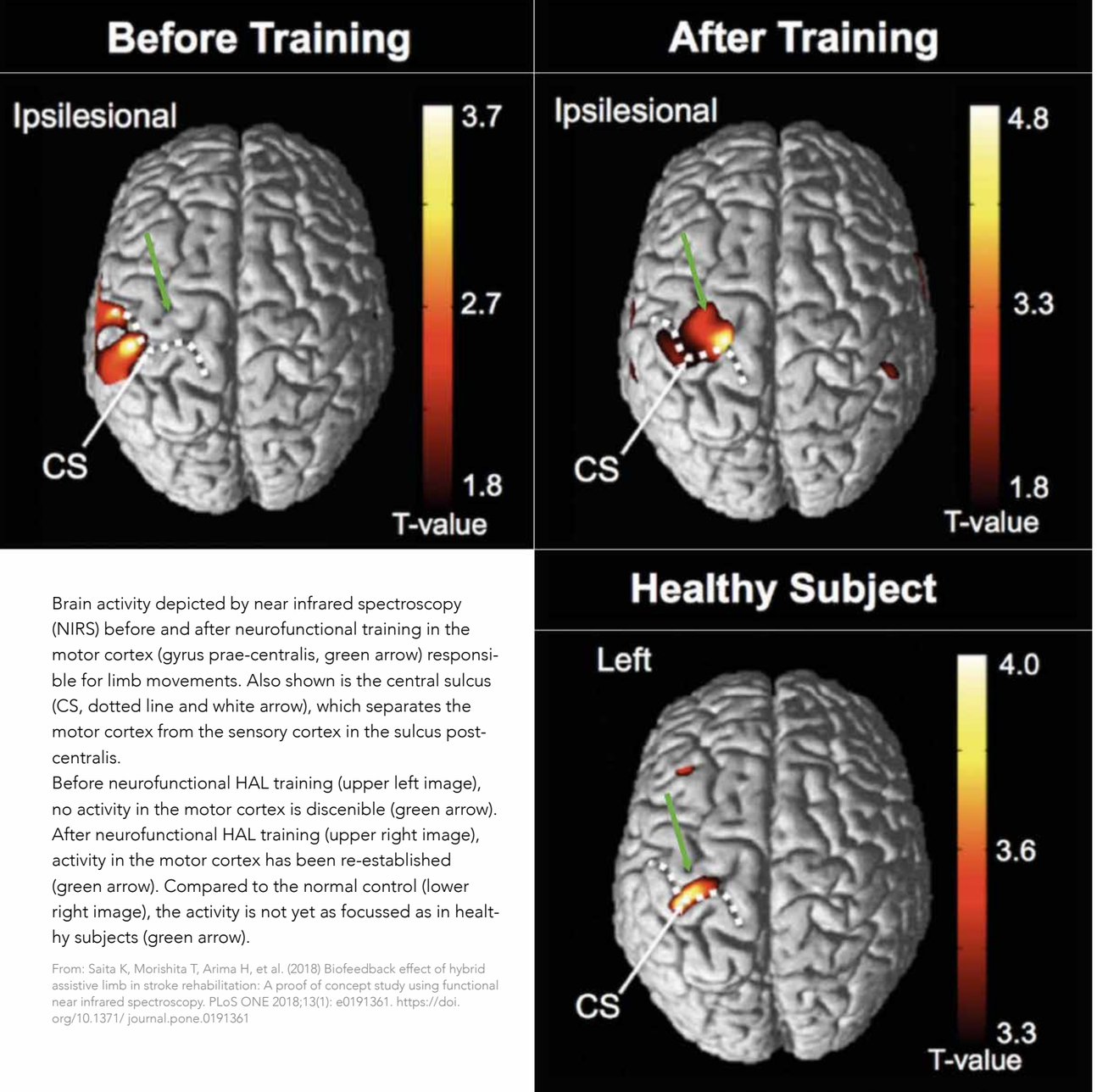
New therapies are now providing hope for better outcomes in patients with SCI. With neuro-regenerative and neuro-functional treatments even patients who have been confined to the wheelchair for years have the potential to walk again.

Whilst in the past it was assumed that the main problem in patients with SCI is at the level of the injured spinal cord, it is now understood that the complex patho-mechanisms involve both the spine and the brain.

SCI leads to disturbances in the functional circuitry of motor and sensory functions. Motor function not only requires signal output from the brain via the spinal cord and peripheral nerves to the muscles, but also sensory input from proprioceptors in muscles, tendons and joints back to the brain. If these feedback-loops are interrupted, as it is during the early phases of SCI, the whole motor system malfunctions.

Neuro-regeneration with stem cells and neuro-functional training can re-establish, at least in part, the normal functional feed-back loops required for motor function, exploiting the significant functional plasticity of the central nervous system.

[2] https://www.physio-pedia.com/American_Spinal_Cord_Injury_Association_(ASIA)_Impairment_Scale



Brain activity depicted by near infrared spectroscopy (NIRS) before and after neurofunctional training in the motor cortex (gyrus prae-centralis, green arrow) responsible for limb movements. Also shown is the central sulcus (CS, dotted line and white arrow), which separates the motor cortex from the sensory cortex in the sulcus post-centralis.
Before neurofunctional HAL training (upper left image), no activity in the motor cortex is discenible (green arrow). After neurofunctional HAL training (upper right image), activity in the motor cortex has been re-established (green arrow). Compared to the normal control (lower right image), the activity is not yet as focussed as in healthy subjects (green arrow).

From: Saita K, Morishita T, Arima H, et al. (2018) Biofeedback effect of hybrid assistive limb in stroke rehabilitation: A proof of concept study using functional near infrared spectroscopy. PLoS ONE 2018;13(1): e0191361. https://doi.org/10.1371/ journal.pone.0191361

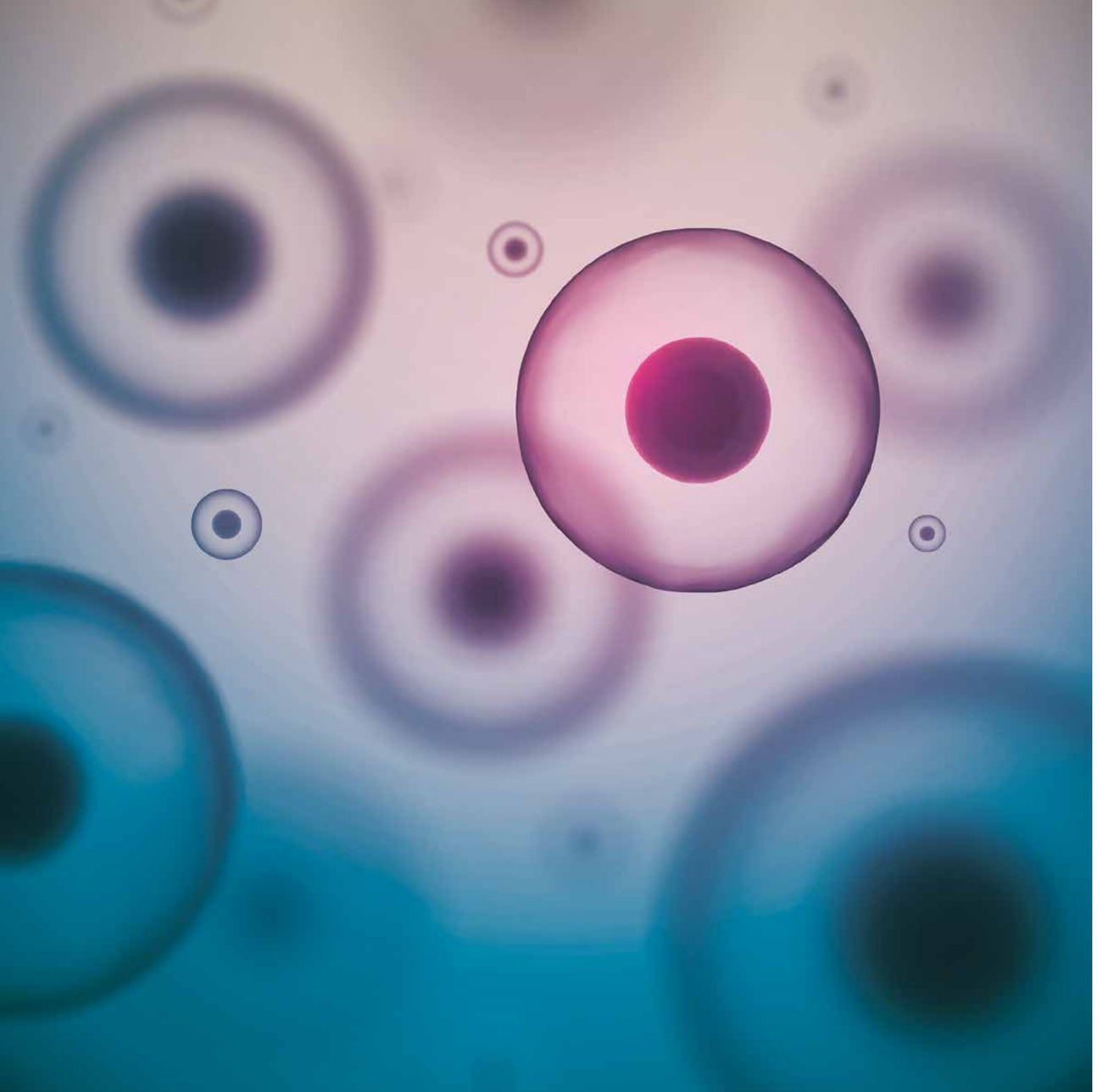
Neuro-Neuro-functional Training with the HAL Robotic Exoskeleton

After a spinal cord injury, nerve signals from the brain to the muscles in the legs (efferent signals) might be to week to make muscles move. But in many patients these nerve signals are still recordable with sensitive electrodes. With the HAL robotic exoskeleton the week nerve signals are amplified and used to activate electrical motors, which in turn move the patient's legs, in an almost natural way.

This generates nerve signals in so-called proprioceptors in the muscles and joints, which are fed back to the brain (afferent signals). These efferent signals originating in the brain, running down the spinal cord and the peripheral nerves and afferent signals from the legs going up the nerves and the spinal cord to the brain form a feed-back loop. In patients with SCI this feedback loop is interrupted and with time degenerates.

Functional brain studies, which can visualize brain activity, have shown that the areas in the motor cortex of the brain (gyrus prae-centralis), which control specific movements of the legs and are normally very focussed on small areas of the motor cortex, "smear out" over larger areas in patients with SCI. This might impede voluntary initiation of motion by deeper functional centres of the brain.

During HAL training, the functional activity is re-focussed onto the original area of the motor cortex. It thus appears that the re-establishment of the feed-back loop, particularly the sensory input from the proprioceptors in the leg to the brain, is an essential component of voluntary motion.



Neuro-Regeneration with Mesenchymal Stem Cell Secretome

Pre-clinical research has elucidated the various beneficial effects of mesenchymal stem cells (MSCs) and their secretome on spinal cord injuries. Whilst the initial assumption that stem cells replace lost nerve cells and thus restore function did not prove to be true, MSCs and their secretome support neuro-regeneration in many other ways.

SCI comprises many mechanisms of injury which result in functional impairment: Besides the immediate death of neurons and glia (support cells) due to the injury, there is delayed cell death by apoptosis (cell suicide), interruption of axons (nerve tracts), loss of vessels and blood supply, inflammation, glial scarring and many others.

MSCs have been shown to reorganise the architecture in glial scarring and by improving the growth of axons supporting the reconnection of nerve tracts across glial scars improving the conductivity of nerve signals in the spinal cord. At the same time, MSCs have been shown to improve the vascularisation and blood supply in damaged areas of the cord by inducing the growth of new blood vessels. This is a critical component in the re-establishment of a more normal micro-architecture of the spinal cord.

Stem Cells and Robotic Exoskeletons: REMCell Therapy – A Novel Approach to Neuro-Rehabilitation

ANOVA Institute for Regenerative Medicine, Germany's pioneering institution for stem cell therapies, and Cyberdyne, the Japanese pioneer in robotic neuro-functional training, have formed an alliance to establish a novel and effective treatment for spinal cord injury: REMCell, Robotic Exoskeleton and Mesenchymel Stem Cell Therapy. REMCell integrates neuro-regeneration (NR) with stem cells and neuro-functional (NF) training with the HAL robotic exoskeleton. They have established what currently constitutes the most promising and probably the most effective way for functional recovery after a spinal cord injury.

A complete course of REMCell Therapy takes 3 months and comprises stem cell harvesting, expansion and secretome production in ANOVA's GMP laboratory and 60 sessions of HAL robotic NF training synchronised with intrathecal NR secretome treatment.

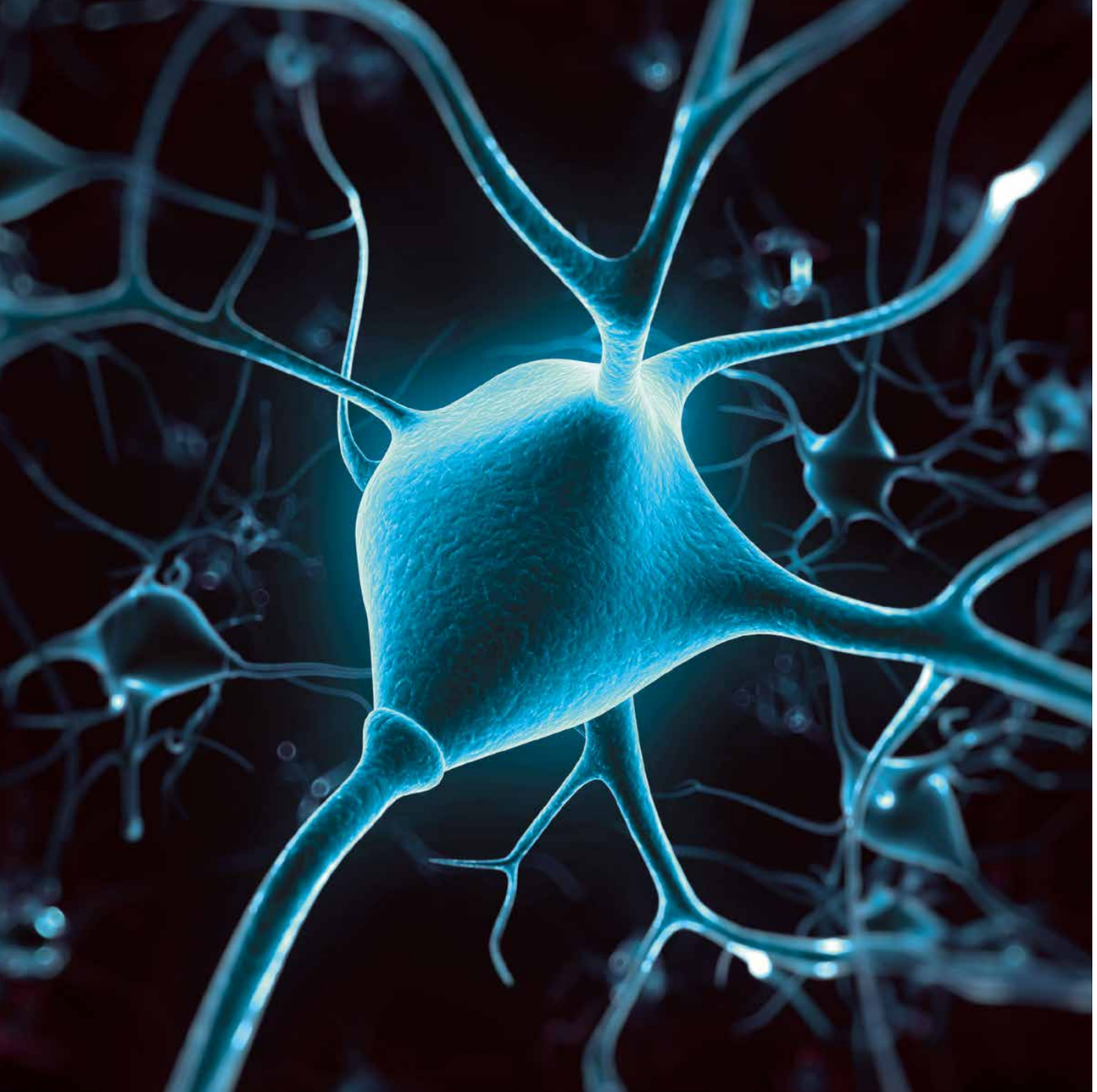
Phase 1 - Evaluation of Suitability for REMCell Therapy

The patients are first evaluated for remaining nerve signals in their legs and whether they are a suitable donor for mesenchymal stem cells. If these tests are positive, the REMCell Therapy can be commenced. Phase one takes a day or two for the patient, and about a week for the results to return from the laboratories.

Phase 2 - Stem Cell Harvesting and Secretome Production

Stem cell therapy requires the harvesting of mesenchymal stem cells (MSC) from the subcutaneous fat, which is done in an out-patient procedure with a mini-liposuction, similar to cosmetic liposuction. This is a minimally invasive procedure and takes approximately 1 hour in the OR, and altogether half a day for the patient. The stem cells are then isolated from the fat and grown in the laboratory.

When a sufficient number of stem cells has been grown, the cells are put under certain conditions, which will optimise the secretome production by the cells. Ten or 20 doses of MSC secretome can be produced and stored for a maximum of two years. The production takes 4 weeks to complete.



Phase 3 - Neuro-Functional Training and Neuro-Regenerative Stem Cell Treatment

Immediately after the stem cell harvesting has been completed, the patient starts with HAL training, 5 days a week with a daily session lasting 1 - 2 hours each. Weekends are free.

After 4 weeks of training, the MSC secretome production is complete and the first infusion of MSC secretome is carried out. Alternative to the intravenous infusion, the MSC secretome can also be injected intrathecally, i.e. into the cerebro-spinal fluid (CSF) surrounding the spinal cord and brain. Depending on whether 10 or 20 doses of MSC secretome were produced, the patient receives infusions/injections every two weeks or weekly.

What therapeutic successes can be expected?

Whilst HAL training by itself has already been shown to be much more effective than conventional neuro-rehabilitation training, the combination with stem cell-based neuro-regeneration promises even better results. Pre-clinical studies of the effect of mesenchymal stem cells and their secretome have shown numerous beneficial effects on the damaged spinal cord tissue, such as the re-organisation of glial scars, improved vascularisation and the promotion of axonal growth.

As for the HAL exoskeleton, research has shown that neuro-functional training improves the patients' independence, especially their ability to walk, significantly. Walking with a rollator, crutches or ortheses became possible for many patients previously confined to the wheelchair.

But there are also other benefits: Patients experienced a decrease in neuropathic pain, positive changes in spasticity, improved sensitivity and, as a result, a reduced risk of pressure sores. After completion of neuromuscular feedback therapy, the successes achieved are maintained as long as the patients actively use their regained mobility in everyday life, i.e. getting out of the wheelchair and walking with a rollator or using crutches.

How Can You Profit from ANOVA's Combined Neuro-Regenerative and Neuro-Functional REMCell Therapy?

If you suffer from spinal cord injury REMCell therapy can improve your motor function, sensation and atutonomic functions such as bladder and bowel control.

In paraplegic patients in whom nerve signals can be detected in the limbs, even if they are too weak to control muscle function, have the best chances for recovery with REMCell therapy. Newer research, however, shows, that even in patients without residual peripheral nerve signals, there is a chance for improvement.

Recent studies have also shown that patients with several other neurological conditions can profit from HAL neuro-functional training and neuro-regenerative stem cell therapy. These conditions include most traumatic, ischaemic and neuro-degenerative disorders of the central nervous system:

- Stroke
- Amyotrophic Lateral Sclerosis - ALS
- Multiple Sclerosis – MS
- Parkinson's Disease

As for SCI patients, all other patient groups must meet appropriate treatment eligibility requirements. For stem cell production, donor suitability must be established.

In order to find out whether you are can profit from **ANOVA's** ground-breaking REMCell therapy talk to our patient care managers. We will evaluate your medical records and assess you on-site.

If you want to get out of the wheelchair, call **ANOVA** now:
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