# Why Stem Cell Technology for Neurodegenerative Diseases Requires a Paradigm Shift

**In this double interview, Johannes de Munter, CEO of Neuroplast, and Professor Dr Boris Kramer, consultant on stem cell biology, explain how alternatives to stem cell approaches, based on a profound biological understanding of neurodegenerative diseases, can give back perspective to patients, before sharing their expectations for the future**

***EBR*: How would you describe the current, mainstream point of view on stem cell therapies?**

**Johannes De Munter:** Today's stem cell therapies are largely based on the replacement of diseased cell populations or the replacement of killed cells, through bone marrow transplantation. Stem cells have the capacity to act and adapt to local circumstances. The underlying assumption is often that we need stem cells from donors, because the patient's own cells are damaged or grow uncontrollably. This is a very logical basis for treatments in oncology or haematology, for example. Those patients benefit from other stem cells, because their own are broken. In that context, it also makes sense to accept accompanying risks of such treatments, because there are no feasible alternatives.

**What challenges do you see?**

**De Munter:** Using stem cells from donors is an amazing scientific achievement. But the behaviour of stem cells is also very complex, with a lot of unknowns. Especially regarding short- and long-term side effects, such as efficacy and effect over time.

**Why do you believe we need a paradigm shift for neurodegenerative diseases?**

**De Munter:** There are different disease mechanisms at play. Neurogenerative conditions are high-impact incurable diseases that affect millions of people worldwide. Neurodegenerative disorders are responsible for the sickness and impaired quality of life of nearly one-fifth of the world population. Those people do not benefit from traditional cell therapies and only have access to symptomatic treatments.

**Can you elaborate on those disease mechanisms?**

**Dr Boris Kramer:** Neurodegeneration is the progressive loss of structure or function of neurons, including their death. This can be caused by trauma, ischemia, or a mixture of genetic and environmental factors. Examples of such conditions are spinal cord injury, frontotemporal dementia, traumatic brain injury, subarachnoid stroke, or amyotrophic lateral sclerosis (ALS).

Even though the causes differ and the diseases may seem unrelated at first glance, many similarities appear that

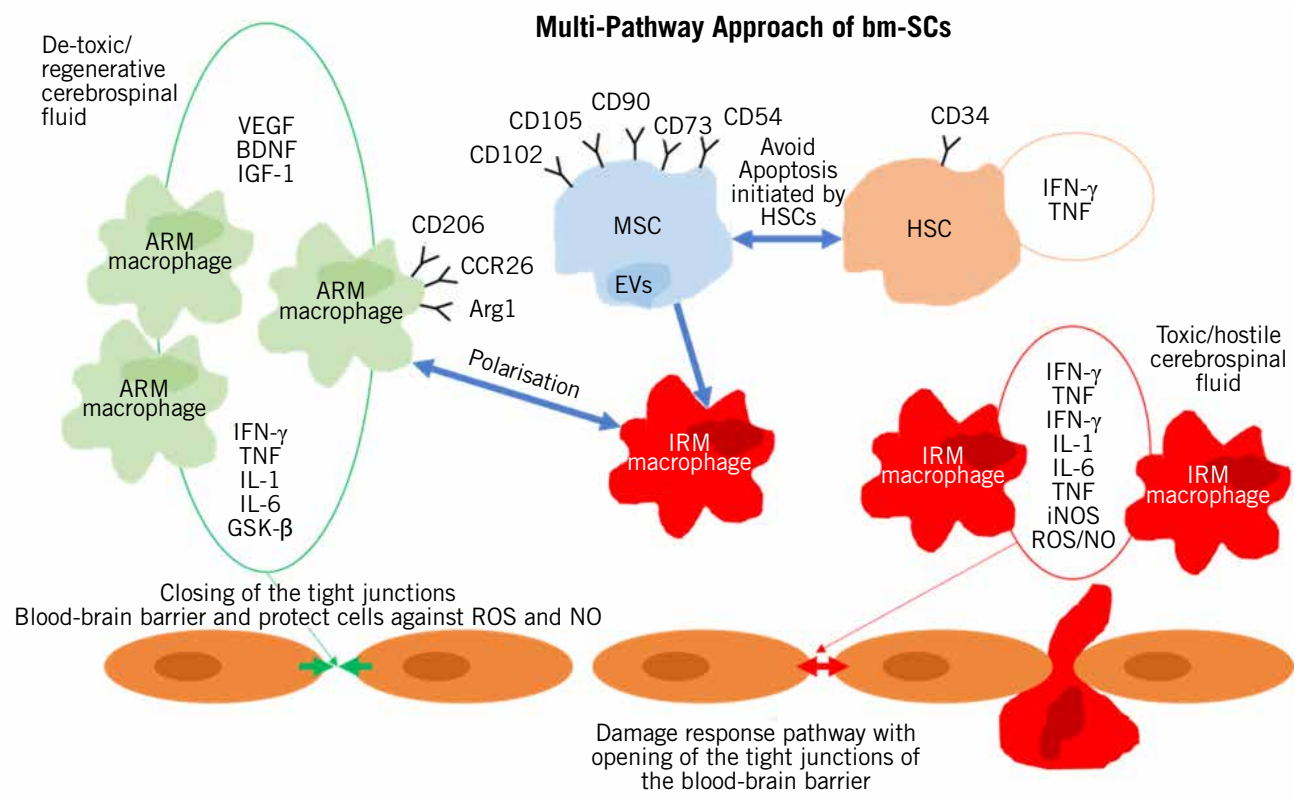



Figure 1: An overview of the interaction of stem cells in the maintenance of a regenerative non-toxic cerebrospinal fluid. The MSCs by cell-to-cell communication polarise the IRM macrophages into ARM macrophages. The ARM macrophages decrease the pro-inflammatory cytokines and enhance the growth factors. ARM macrophages gen-expression for CD206, CCR26 and Arg1.
**Abbreviations**: ARM: activated response microglia; BDNF:Brain-derived neurotrophic factor; EVs: Extracellular vesicles; GSK-β: glycogen synthase kinase-3 beta; HSC: haematopoietic stem cell; IGF-1: insulin-like growth factor-1; IFN-γ: Interferon-gamma; IL-1: Interleukin-1; IL-6: Interleukin-6; iNOS: inducible nitric oxide synthase; IRM: Interferon Response Microglia; MSC: mesenchymal stem cell; NO: nitric oxide; ROS: reactive oxygen species; TNF: tumour necrose factor; VEGF: vascular endothelial growth factor (1)

relate these processes to one another on a sub-cellular level: unprogrammed cell death, boosted by secondary inflammation.

Discovering these similarities offers hope for adequate therapeutic interventions for those millions of patients with unmet needs.

**How do you translate the disease mechanisms to an alternative view on stem cell therapy?**

**Kramer:** Unlike other diseases that require stem cell therapy, the regenerative capabilities of the neurodegenerative patient's own cells are still intact. Therefore, there is no need to transplant stem cells from donors and run unnecessary risks of rejection. It makes more sense to leverage the patient's own cells.

**How do we do that – leverage the capabilities of the patient's own cells?**

**De Munter:** We distinguish three foundational principles in the development of effective treatments for neurodegenerative diseases.

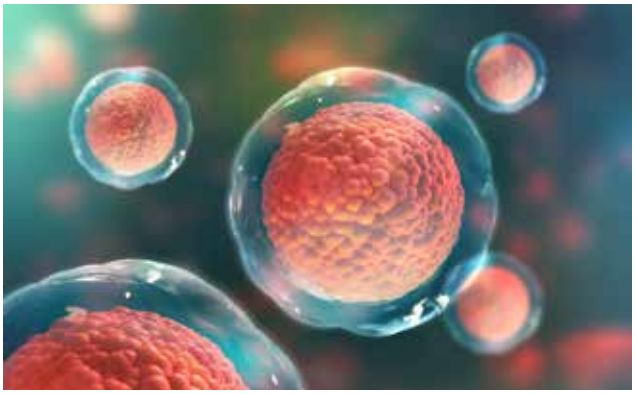
Firstly, a treatment should be autologous, meaning they are based on the patient's own cells. Contrary to allogeneic treatments, the risk for negative immune responses is nearly non-existent.

Secondly, no substantial cell manipulations should take place, to keep the potential of naïve cells. As mentioned before, the regenerative capability of the cells from these patients are not broken. They just need to be guided to the right place.

The final principle is intrathecal application. Regenerative mechanisms of the patients' cells cannot reach the central nervous system easily, due to the blood-brain barrier. Intrathecal application delivers the treatment where it matters, and is, therefore, more effective than intravenous application or drugs.

**What evidence do you have that this is the right approach?**

**Kramer:** The Neuroplast technology is currently subject to a Phase II clinical trial for traumatic spinal cord injury and has been awarded with an orphan drug designation for this disease. Safety has already been determined in a 90-day



open Phase I study in end stage chronic traumatic spinal cord injury patients.

**Do you know of other studies that point in the same direction of looking at stem cell treatments for these conditions?**

**De Munter:** There are two noteworthy studies. In 2021, Honmou and his team published their research on the intravenous infusion of cultured autologous stem cells in spinal cord injury patients (2). They reported no serious adverse events and neurological improvement in 12 of the 13 included patients six months after treatment.

The significant difference is that Honmou studied intravenous delivery, whereas one of our foundational principles is intrathecal application. It's very difficult to effectively reach the central nervous system through intravenous delivery, due to the blood-brain barrier.

The other study is from 2016, by Kakabadze and his co-researchers (3). They successfully finished a Phase I trial of autologous bone marrow stem cell transplantation in spinal cord injury patients. They reported feasibility and safety, and improvement of motor and sensory functions in 50% of the included patients with complete motor deficits and paraplegia.

**What are your expectations for the future?**

**De Munter:** Given the evidence and the progress we are making, we are confident that we are on the right track to substantially contribute to science and patients. It would be wonderful if, down the line, this alternative vision of stem cell technology for neurodegenerative diseases results in a plethora of treatments for all those patients that have no effective treatments available to them today.

> *It's very difficult to effectively reach the central nervous system through intravenous delivery, due to the blood-brain barrier*

*References*

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**Johannes de Munter**, MD, PhD, is founder of and CEO at **Neuroplast**. Johannes worked for over 20 years to find new opportunities to help spinal cord injury patients, after being confronted with their tremendous impact on people as an Emergency Health Care Physician and General Practitioner. He holds a PhD in autologous stem cells in neurodegenerative disorders at University Maastricht, Department of Mental Health and Neuroscience, the Netherlands, and worked for 18 years as a public health physician, responsible for infection disease control and epidemiology in Maastricht, the Netherlands.

**Professor Dr Boris Kramer** is consultant on stem cell biology.