



Fundamenteel onderzoek op herstel van ruggenmergletsels

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Ruggermergtrauma – huidige onderzoeksprioriteiten (1)

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Correspondence

Top ten research priorities for spinal cord injury

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Onderzoeksprioriteiten opgesteld op basis van vragenlijst aan patiënten, artsen en zorgverstekkende diensten !



Ruggermergtrauma – huidige onderzoeksprioriteiten (2)

Panel: Top ten research priorities for spinal cord injury

- 1 Does activity based rehabilitation, including functional electrical stimulation

Resulteert stamceltherapie in een verbeterd herstel en is dit afhankelijk van het type ruggermergtrauma (acuut of chronisch, partiële of volledige dwarslaesie)?

- 4 What bladder management strategy is most effective in reducing the number of urinary-tract infections and secondary complications?
- 5 Does early mobilisation or a period of 4–6 weeks of physically active bed rest (ie, physiotherapy exercises whilst lying in bed) result in improved patient outcomes after surgical spinal column stabilisation?
- 6 Does discharge from a hospital to a physically enabling environment improve quality of life?
- 7 Does the provision of specialist rehabilitation services, which includes multidisciplinary team planning, improve health and wellbeing?
- 8 Do interventions such as controlled fibre and fluid intake improve bowel function and quality of life?
- 9 Which are the effects of ageing on the development of complications, such as spasticity and bladder and bowel incontinence, and need for home-based support?
- 10 Does early diagnosis and treatment lead to improved outcomes for people with (a) cauda equina syndrome and (b) transverse myelitis (including relapses)?

Overgenomen uit: van Middendorp JJ et al. et al. The Lancet Neurology 2014



Commerciële stamceltherapie voor ruggenmergtrauma (1)



Lijst van bedrijven / organisaties die "commerciële" stamceltherapieën aanbieden

Unproven Therapies Identification	Location	Comments
CELLS4HEALTH/ X-CELL CENTER www.cells4health.com Mr Kleinbloesem	Current: LEBANON Past (locations shut down by local authorities): Turkey ; Azerbaijan ; Cologne & Dusseldorf, Germany	Update 2012: After the X-cell centers in Germany were shut down by the German Health authorities in 2011 (NEWS), X-cell center has taken back its original name "Cells4health" and is now offering Stem Cell treatments in Lebanon. CEO, Mr Kleinbloesem, is former CEO and founder of x-cell center in Germany. Cells4Health have a record of stem cell therapies administered in Turkey and Azerbaijan which have resulted in a loss of function for at least three patients. Although the CELLS4HEALTH/ X-CELL website and brochures claim efficacy of their treatment for SCI, no data is made available to the scientific community for peer review. A clinical trial was planned to take place as of 2011 to underpin the claimed efficacy but has not taken place so far. Type of therapy: Bone Marrow Autologous Stem Cells.
BEIKE BIOTECH www.beikebiotech.com	Shenzen, China	Type of therapy: Umbilical Cord Autologous Stems Cells & Intrathecal Bone Marrow Autologous Stem Cells. Patients are recruited via http://www.stemcellschina.com where anecdotal testimonials are published. However, there is no scientific efficacy data published for their Spinal Cord Injury patients.
NUTECH MEDIWORLD dr Geeta Schoff www.nutechmediworld.net	Delhi, India	Type of therapy: Embryonic Stem Cells Only anecdotal testimonials available from a handful of patients. No scientific data is published by NuTech Mediworld.
Dr HUANG Bijjing- China	Beijing, China	Type of therapy: Olfactory Ensheathing Cells (OEC) and Schwann Cells A double blind randomized clinical trial was performed in 2008-2009 although no results have been published as yet.
Dr Carlos LIMA Lisbon- Portugal	Lisbon, Portugal	Type of therapy: Olfactory Mucosa Autografts Dr Lima made the following <u>publication</u> in Sept 2009. The procedure is proven to be safe - However, the efficacy is not yet proven.
DR AL ZOUBI www.stemcellsarabia.net	Jordan	Type of therapy: Autologous Adult Stem Cells Transplanted purified stem cells into eight patients (6 males and 2 females) with complete thoracic level injuries. The stem cells were isolated from the blood of the patient (i.e., autologous). There is currently no scientific data showing efficacy of the treatment.

NICHI-IN CENTRE for Regenerative Medicine JAPAN INDIA www.ncrm.org	Japan, Chennai India	Type of therapy: Autologous Bone Marrow Stem Cells Only anecdotal information is available in patient testimonials.
SPECTRUM CELL CLINIC Dr Sunil Waghmare MUMBAI	Mumbai, India	Type of therapy: Autologous Bone Marrow Stem Cells using multiple route techniques (anterior spinal artery, intrathecal and intra-lesional). Only one anecdotal testimonial to date. No scientific data for efficacy.
THERAVITAE CO., Ltd. Headquarter in Israel Procedures in Bangkok www.theravitae.com	Bangkok, Thailand & Israel	Type of therapy: Autologous Adult Stem Cells
MEDISTEM INC/ STEM CELL INSTITUTE Dr Thomas Ichim http://www.cellmedicine.com/	Panama City	Type of therapy: Autologous Bone Marrow Stem Cells and Human Umbilical Cord Blood. Cells are administered intravenously and intraethically. A course of 16 injections over the 4-week period is standard. Anecdotal patient testimonials are available at http://www.cellmedicine.com/testimonials/?catid=14
TIANTAN PUHUA HOSPITAL www.puhuachina.com	Beijing, China	Type of therapy: Autologous Bone Marrow Stem Cells
VIGENDO Singapore www.vigendo.com	Singapore	Type of therapy: Umbilical Cord Blood derived Stem Cells Cells are administered by one of a combination of a) transplanting directly into the site of injury b) intravenous injection c) intraethically via lumbar puncture or d) directly into the brain via a stereotactic brain injection. Anecdotal data available showing 98 patients out of 136 have shown significant results using the CT-guided stem cell transplant.
STEM CELL REJUVENATION CENTRE Phoenix- USA www.stem-cell-center.com/	USA	Type of therapy: Autologous Adipose Stroma-derived Stem Cells Cells are administered intraethically via lumbar puncture. To date there has not been any evidence of efficacy via scientific or anecdotal channels.
Medra Inc www.medra.com/	Dominican Republic, US, Georgia and Germany	Type of therapy: Human Fetal Stem Cells. Cells are administered intravenously (blood stream) or subcutaneously (under skin). There are number of anecdotal patient testimonials on the website. There is very little evidence of efficacy. There is also a BBC report on this clinic. See here :



Commerciële stamceltherapie voor ruggenmergtrauma (2)

The screenshot shows the Cells4Health website. The header includes the logo and navigation links: Home, Stem Cell Therapy, Treatment, Cells4Beauty, News, and Apply Now. The main content area is titled 'Spinal Cord Injuries' and 'Stem Cell Treatment of Spinal Cord Injuries'. It contains text explaining that a spinal cord injury usually begins with a sudden, traumatic blow to the spine, which fractures or dislocates vertebrae. The damage begins at the moment of injury when displaced bone fragments, disc material, or ligaments bruise or tear into spinal cord tissue. It also mentions that most injuries to the spinal cord don't completely sever it, and that an injury is more likely to cause fractures and compression of the vertebrae, which then crush and destroy the axons, extensions of nerve cells that carry signals up and down the spinal cord between the brain and the rest of the body. An injury to the spinal cord can damage a few, many, or almost all of these axons. Some injuries will allow some complete recovery, others will result in complete paralysis. It further states that at present, standard spinal cord injury care focuses on urgent emergency care, which is comprised of medications designed to reduce inflammation, immobilization designed to stabilize and align the spine, and surgery to remove bone fragments, foreign objects, and damaged discs or vertebrae which compress the spine. By the time patients leave the hospital, their doctors have given up on the possibility of repairing their damaged spinal cords. Consequently, patients are assigned to rehabilitation to teach them how to live with their disabilities. The website also mentions 'The Cells4Health Spinal Cord Injury Treatment' and 'Diagnostic and Physical Assessment'.

The screenshot shows the 'Treatment Contract' document. It begins with the header 'Treatment Contract' and the Cells4Health logo. The text states: 'Cells4Health GmbH, Baarenstrasse 112, 4302 Zug, Switzerland (hereinafter referred to as "Cells4Health"), and _____ (hereinafter referred to as the "Patient") have concluded the following treatment contract:'. The contract is divided into sections: 1. Subject of contract, 2. Remuneration, and 3. Clarification. Section 1 includes a list of treatments: Angiography, Angioplasty, Intraventricular Surgery, Intramuscular application, Intravenous, Joint Puncture, Lumbar Puncture, Retrobulbar application, Retinal application, and Spinal Catheter. Section 2 includes a list of services: Angiography, Angioplasty, Intraventricular Surgery, Intramuscular application, Intravenous, Joint Puncture, Lumbar Puncture, Retrobulbar application, Retinal application, and Spinal Catheter. Section 3 includes a list of conditions: a) The harvested stem cells are processed in a tissue facility approved by one of the responsible authorities pursuant to Art. 2 No. 10, b) Both facilities work in compliance with the principles of good Manufacturing practice in the sense of Art. 3 Para. 1 of the AMWHV, c) The remuneration is to be paid in full even if the treatment does not take place for reasons in the Patient's sphere of influence, d) The Patient confirms that, before signing this contract, he/she received comprehensive information from Cells4Health through a doctor regarding the course, prospective duration, scope and possible risks and side effects of treatment with adult stem cells, e) The Patient confirms that, before signing this contract, he/she was informed that successful outcome of the treatment cannot be guaranteed.

The screenshot shows the 'Price list' document. It begins with the header 'Price list' and the Cells4Health logo. The list includes the following items and prices:

Treatment	Price
Treatment Lumbar Puncture	10.945,- Euro
Child iv mannitol or LP	10.945,- Euro if necessary anesthesia included
Angiography - one organ	13.145,- Euro
- extra organ in same treatment plus	1.850,- Euro
Cardio angio	16.445,- Euro
MS, Parkinson and ALS programme - injection via angio incl dilatation	16.445,- Euro
- plus iv mannitol extra collection	20.845,- Euro
Lumbar catheter	15.745,- Euro
Brain surgery stereo tactic approach - Private room plus	27.445,- Euro 5.500,- Euro
SCI Surgery - Private room plus	38.445,- Euro 5.500,- Euro
Retrobulbar injection plus mannitol	13.145,- Euro
Direct injection (knee)	13.145,- Euro
Intra venous injection (with or without mannitol)	9.845,- Euro
Repeat	550,- Euro
Extra cell collection - plus	3.300,- Euro

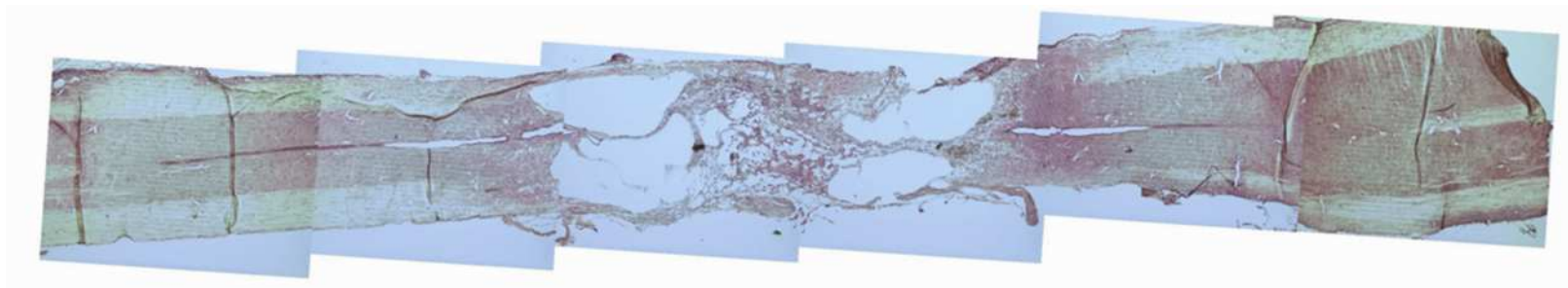
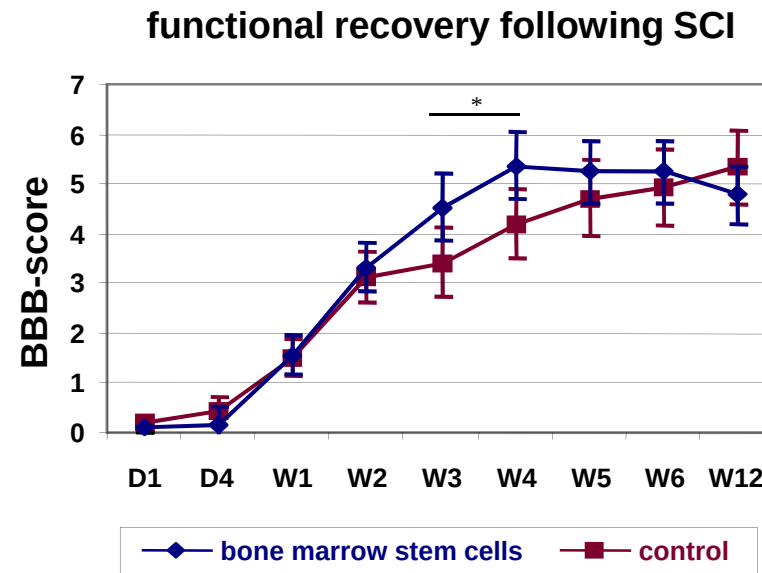
Quote from website: "Almost 60% of the spinal cord injury patients treated with stem cells show improvement."

Quote from treatment contract: "The patient confirms that, before signing this contract, he/she was informed that successful outcome of the treatment cannot be guaranteed."

Quote from (old) price list: "SCI surgery 38.445 Euro. Private room 5000 Euro."



Beenmergstemcellen ter behandeling van ruggenmergtrauma



Kan celtherapie bijdragen tot herstel na ruggenmergtrauma ?



Spinal Cord (2008) 46, 532–539
© 2008 International Spinal Cord Society All rights reserved 1362-4393/08 \$30.00
www.nature.com/sc

REVIEW

Can cell therapy heal a spinal cord injury?

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¹Division of Clinical Pharmacotherapy, University of Antwerp, Antwerp, Belgium; ²Centre for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium and ³Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute (VIDI), University of Antwerp, Antwerp, Belgium

Study design: Literature survey.

Objectives: To summarize and discuss current possibilities and success rates for the treatment of spinal cord injury in animal models.

Settings: University of Antwerp, Belgium.

Methods: We searched Pubmed for publications from 1997 onwards. Seven older papers were used for completion of data.

Results: Despite major progress in pharmacological and surgical approaches, a spinal cord injury still remains a very complex medical and psychological challenge, both for the patients and their relatives, as well as for the involved physicians, with currently no existing curative therapy. For a future efficient treatment, one has to consider and combine four main approaches: (1) tissue or cell transplantation, (2) providing growth-stimulating factors (neurotrophic factors), (3) blocking factors which inhibit neural regeneration and (4) modulation of inflammatory response following spinal cord injury.

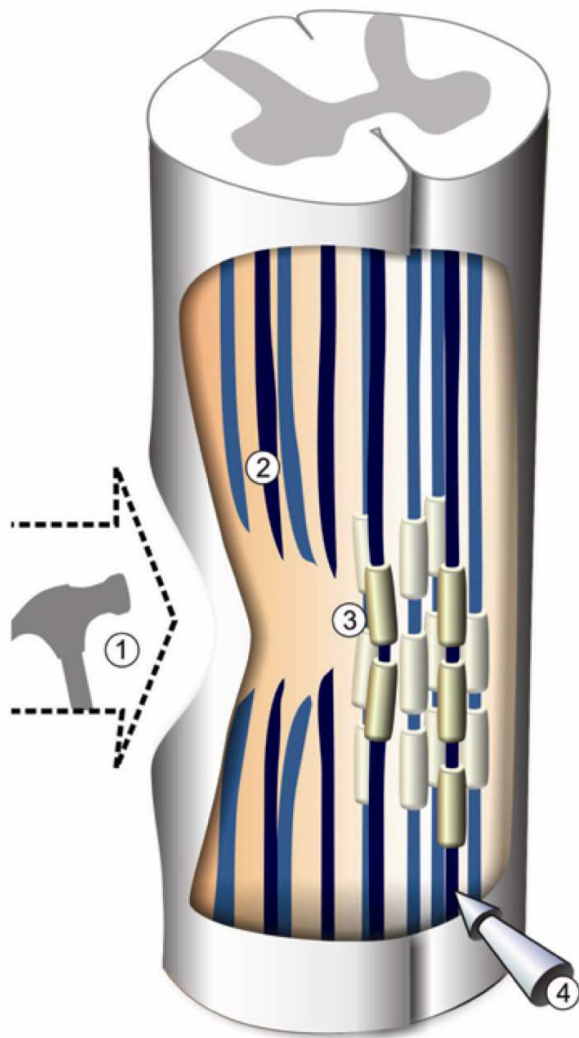
Conclusions: Although different treatment options have proven to be successful in animal models, they also provide a realistic view on a complex therapeutical approach, which needs to be further investigated in many carefully designed animal studies before human applications can be considered.

Spinal Cord (2008) **46**, 532–539; doi:10.1038/sc.2008.13; published online 18 March 2008

Keywords: spinal cord injury; cell transplantation; neurotrophic factors; endogenous neural regeneration; inflammation; clinical trials



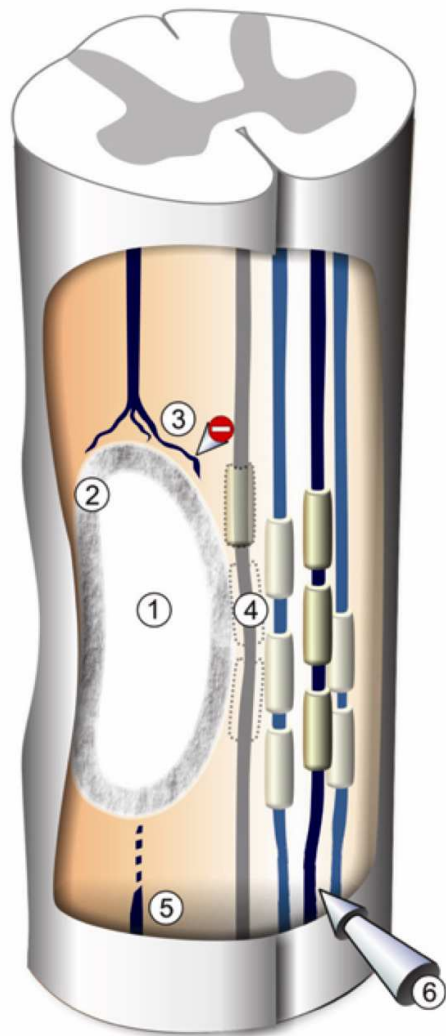
Ruggermergtrauma – acute fase



1. **Directe impact**
2. **Vernietigde axonen**
3. **Beschadigde axonen**
4. **Inflammatie**



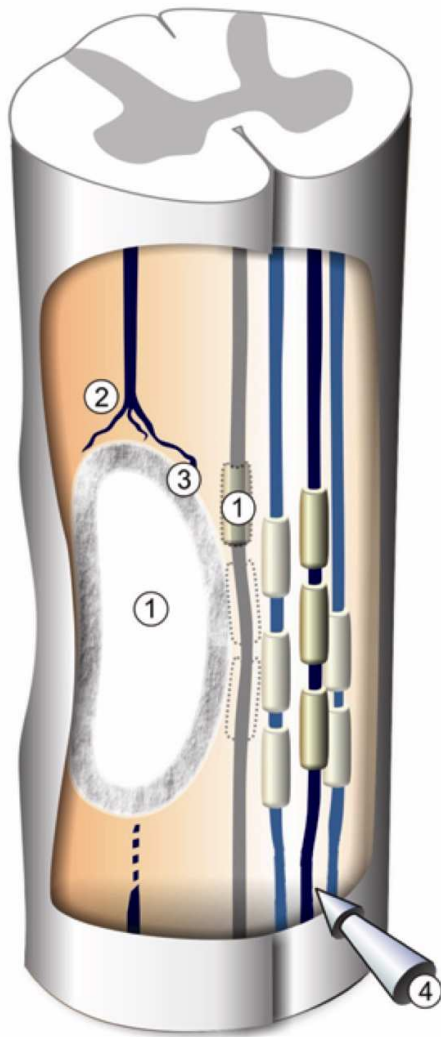
Ruggermergtrauma – chronische fase



1. **Centrale caviteit**
2. **Wondweefsel**
3. **Inhibitie axonale regeneratie**
4. **Demyelinatie**
5. **Afsterven axonen**
6. **Inflammatie**



Ruggermergtrauma – fundamenteel onderzoek



- 1. Cel- en weefseltransplantatie**
 - Adulte en embryonale stamcellen
- 2. Blokkering inhibitie van axonale groei**
 - Inhibitie van NogoA
- 3. Stimulatie axonale regeneratie**
 - Neurotrophe factoren
 - Chondroitinase ABC
- 4. Modulatie van inflammatie**
 - Regeneratie-bevorderende immuunresponsen



Cel- en weefseltransplantatie (1)

“gepubliceerde succesvolle (?) preklinische studies”

- **Celtype:**
 - Beenmergstamcellen
 - Neurale stam/progenitor cellen
 - Mesenchymale (stam)cellen
 - Embryonale stamcellen / IPSC
 - Olfactory ensheathing cells
 - Schwann cellen
- **Route van administratie:**
 - Intraveneus
 - Intrathecaal
 - Intraspinaal
- **Tijdstip van administratie:**
 - Acuut
 - Chronisch
- **Resultaat:**
 - Functioneel herstel
 - Morfologisch herstel
- **Mechanisme:**
 - Celintegratie
 - Immunomodulatie
 - Endogene regeneratie
- **Bemerkingen:**
 - ***Geen standardisatie ...***
 - ***Lage reproduceerbaarheid ...***
 - ***Mechanisme onduidelijk ...***
 - ***Weinig vervolgstudies ...***
 - ***...***



Cel- en weefseltransplantatie (2)

“gepubliceerde succesvolle (?) klinische studies”

Table 6: Clinical spinal cord injury trials using cell therapy.

Transplanted cell type	SCI model	Safety	Neuronal Regeneration and functional recovery	Inflammation repression	Reference
ESCs-OPCs	Phase 1, ASIA Scale Type A	Yes	—	—	[17]
OECs	171 Patients	Yes	Yes	—	[80]
UCMSCs	1, T11-12, ASIA Scale Type A	Yes	Yes	—	[81]
UCMSCs + CD34 ⁺ HSCs	L1, ASIA Scale Type A	Yes	Yes	—	[82]
BMMSCs	ASIA Scale Type A	Partial (spasticity/neuropathic pain)	Yes	Partial	[83]
BMMSCs	ASIA Scale Type A/B/C	Yes	Yes	Partial	[84–86]
SCs	ASIA Scale Type A/B/C	Partial	Yes	—	[87–89]

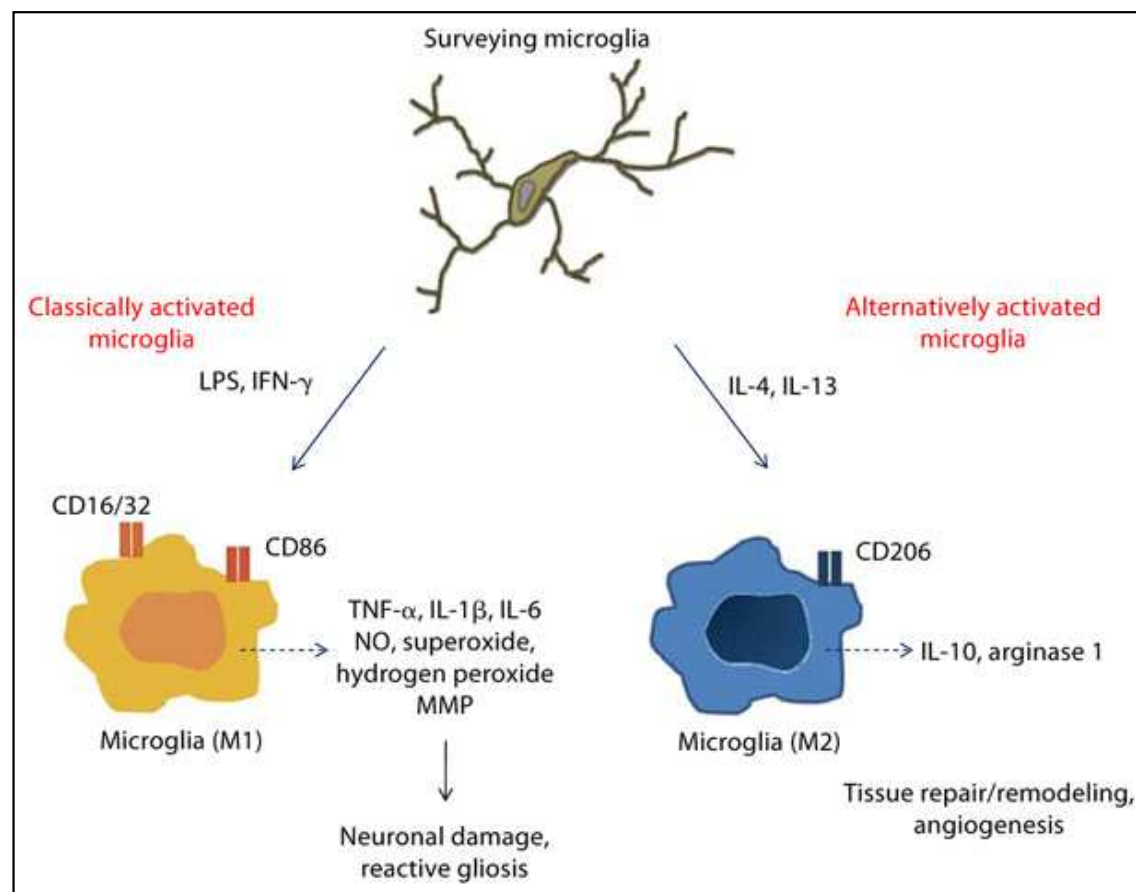
Overgenomen uit: Sabapathy V et al. Stem Cells International 2015

Momenteel enkel fase 1 studies die “veiligheid” mogen suggereren ...

Functioneel herstel onduidelijk ... (althans niet de “holy grail”)



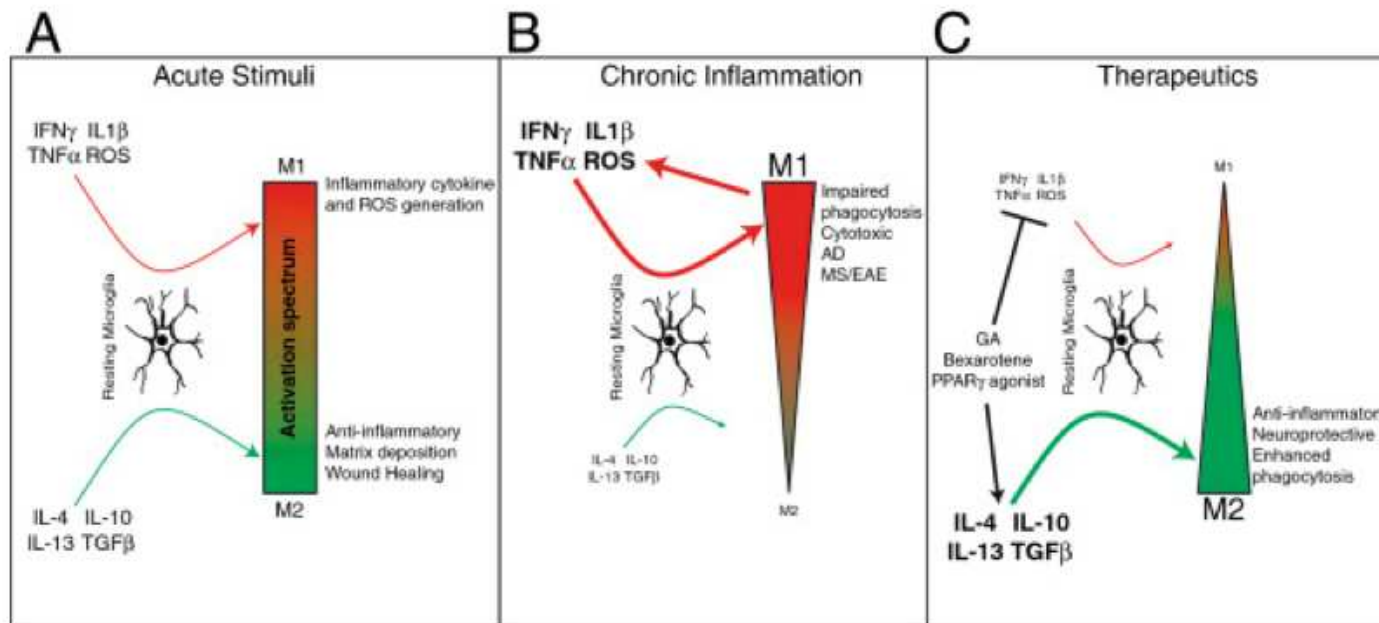
Neuroinflammatie – huidige denkpiste (1)



Overgenomen uit: Czeh M et al. Developmental Neuroscience 2011;33:199–209



Neuroinflammatie – huidige denkpiste (2)



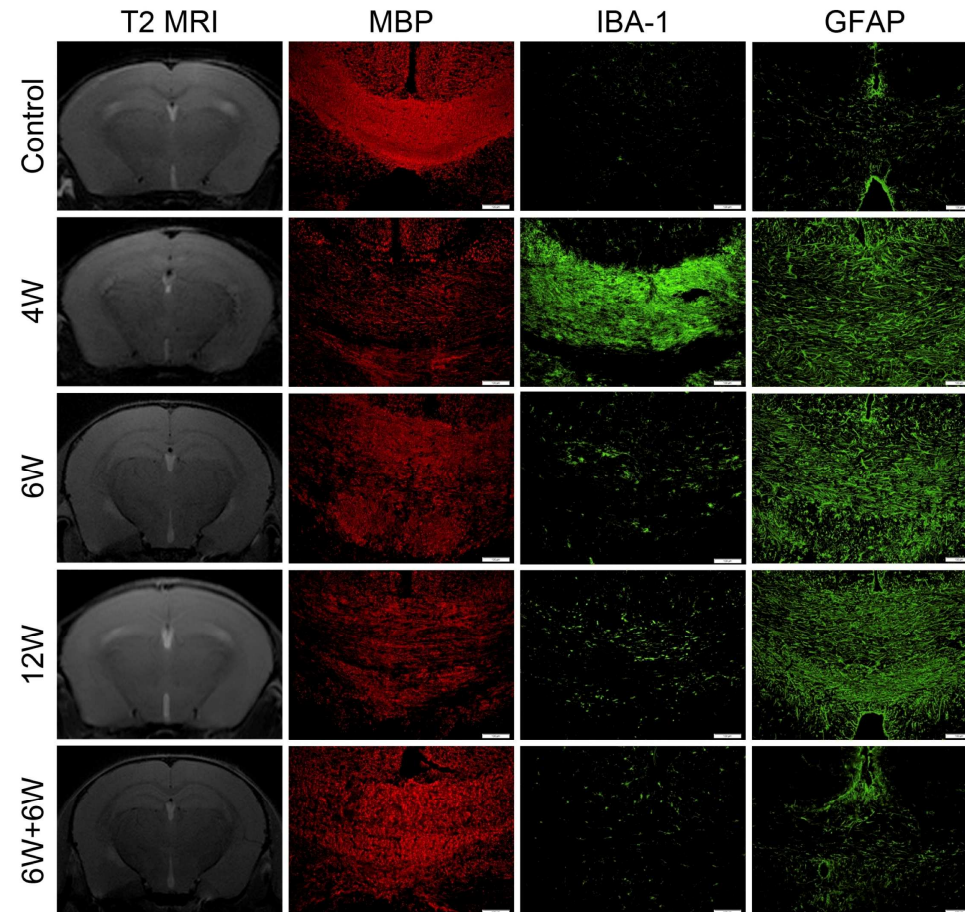
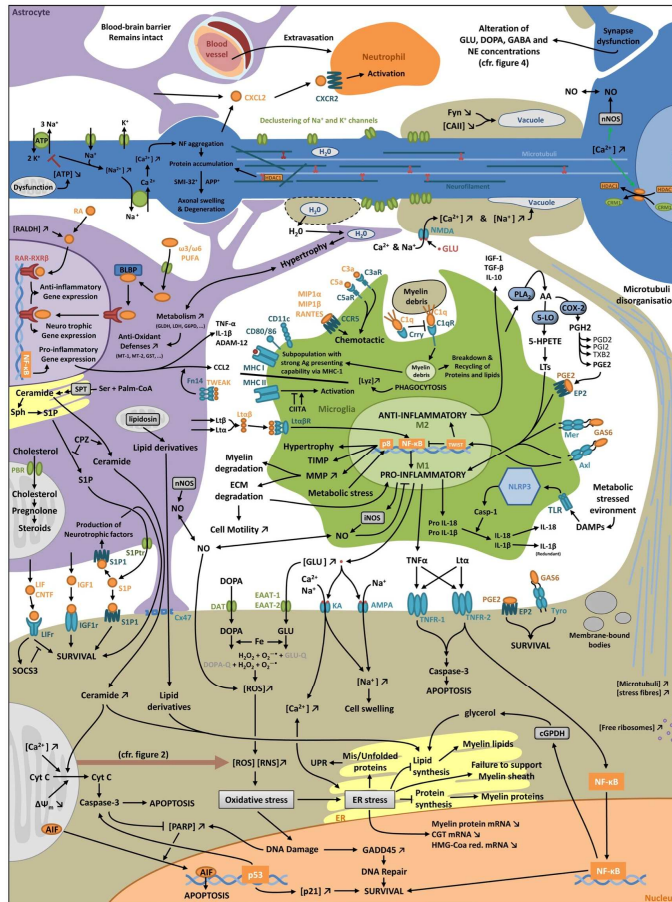
Overgenomen uit: Cherry JD et al. Journal of Neuroinflammation. 2014; 11: 98.

Wat met corticosteroiden (methylprednisolone) ?

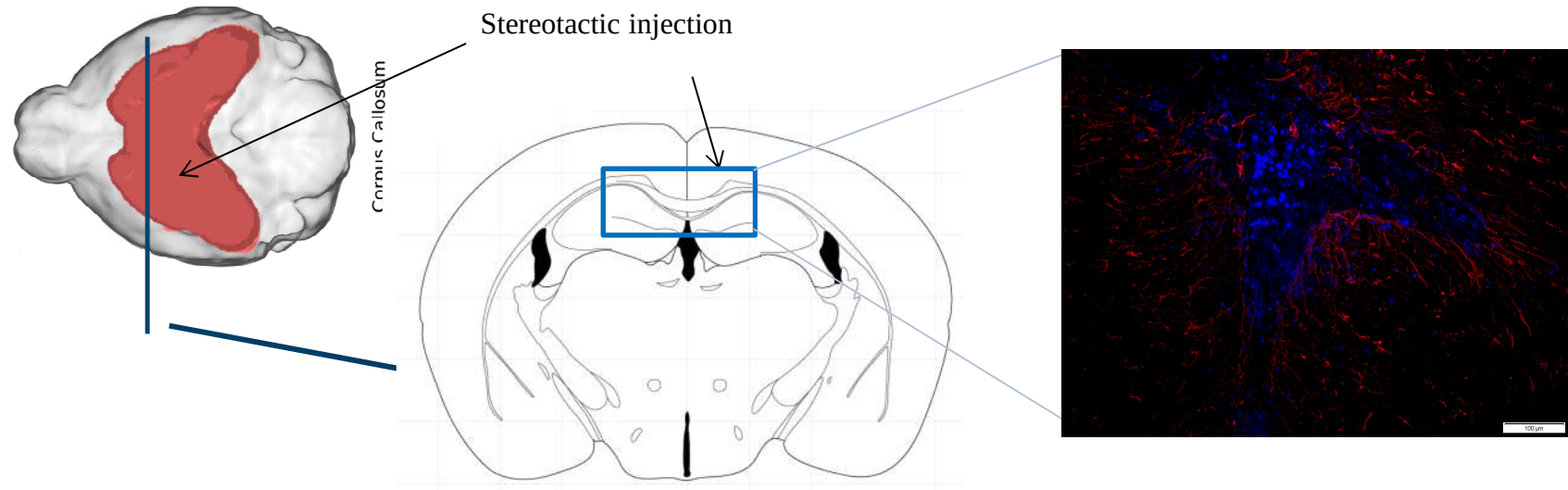
Kunnen we de M1/M2 balans moduleren in vivo ?



Het cuprizone muis model voor CZS inflammatie en demyelinatie



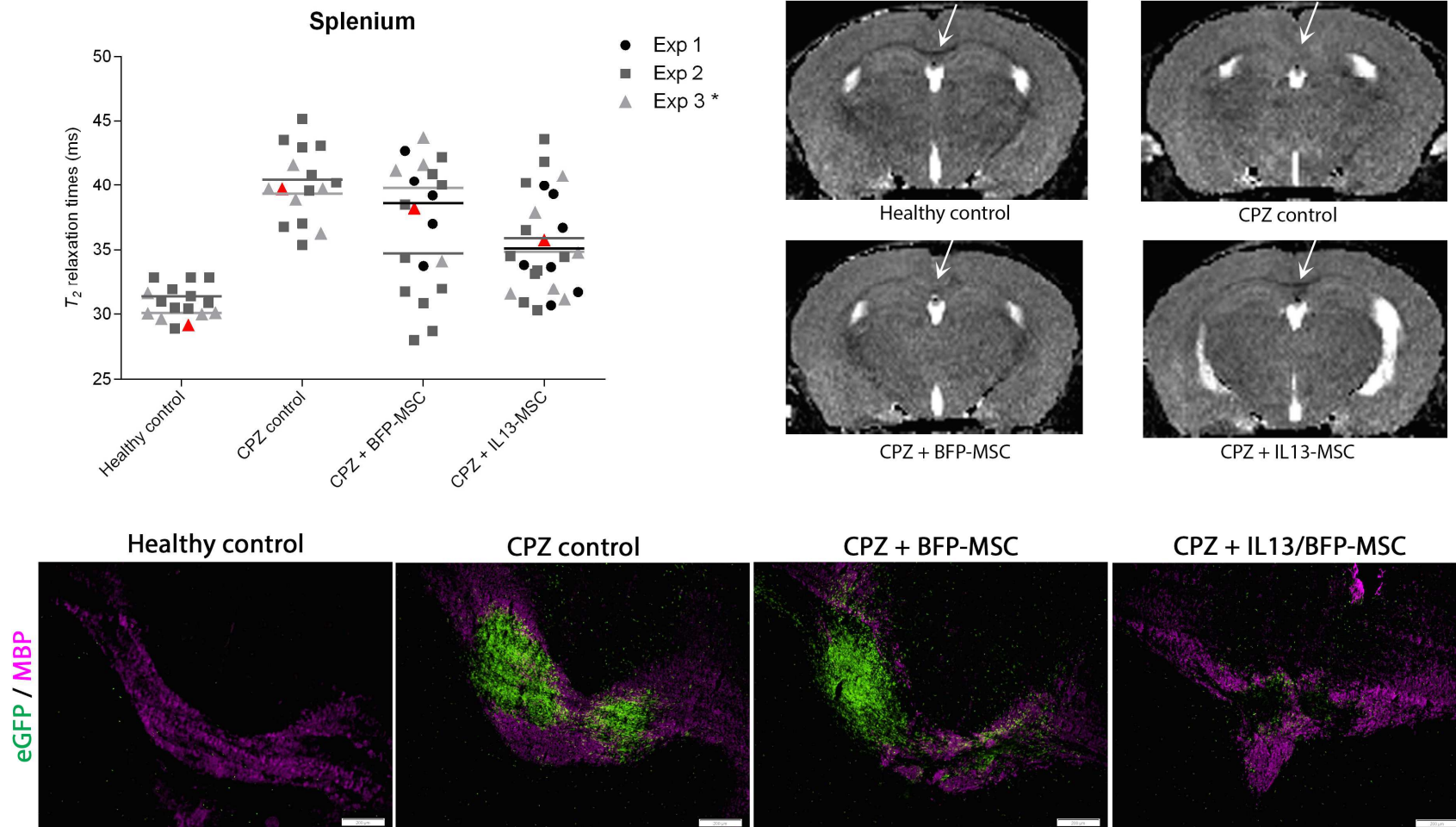
Transplantatie van IL13-producerende stamcellen in CPZ model (1)



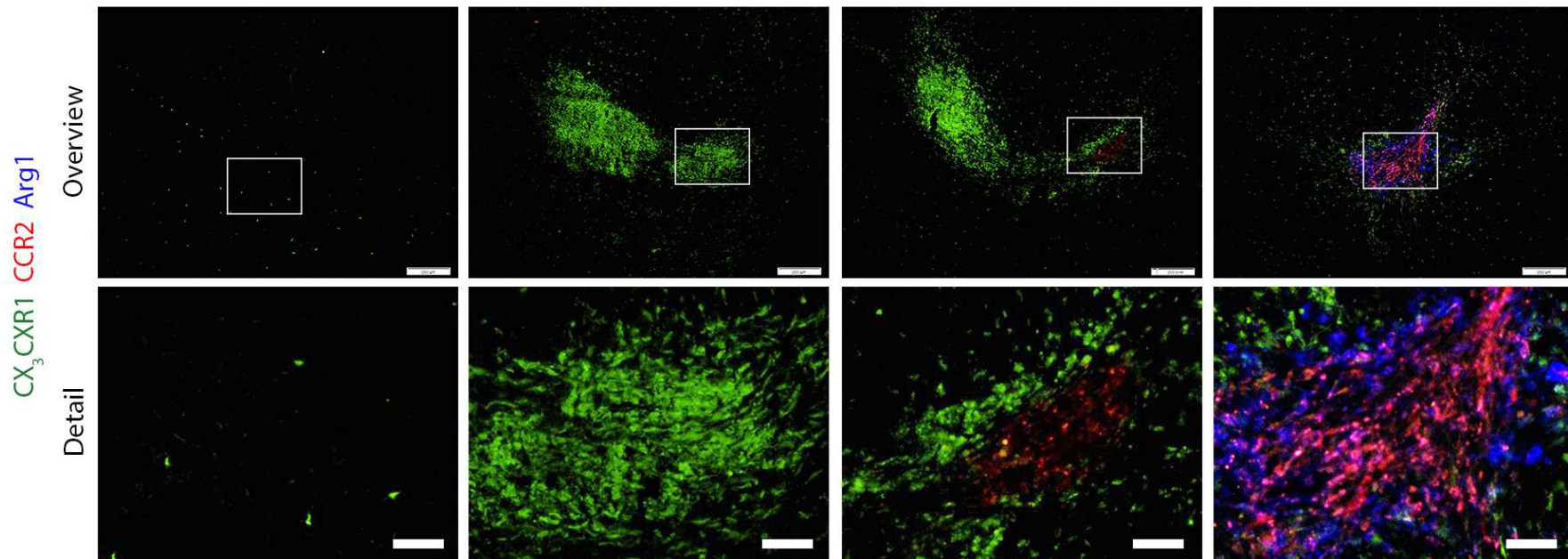
implantatie van syngeneische MSC getransduceerd met een lentivirale vector coderend voor interleukine (IL)-13



Transplantatie van IL13-producerende stamcellen in CPZ model (2)



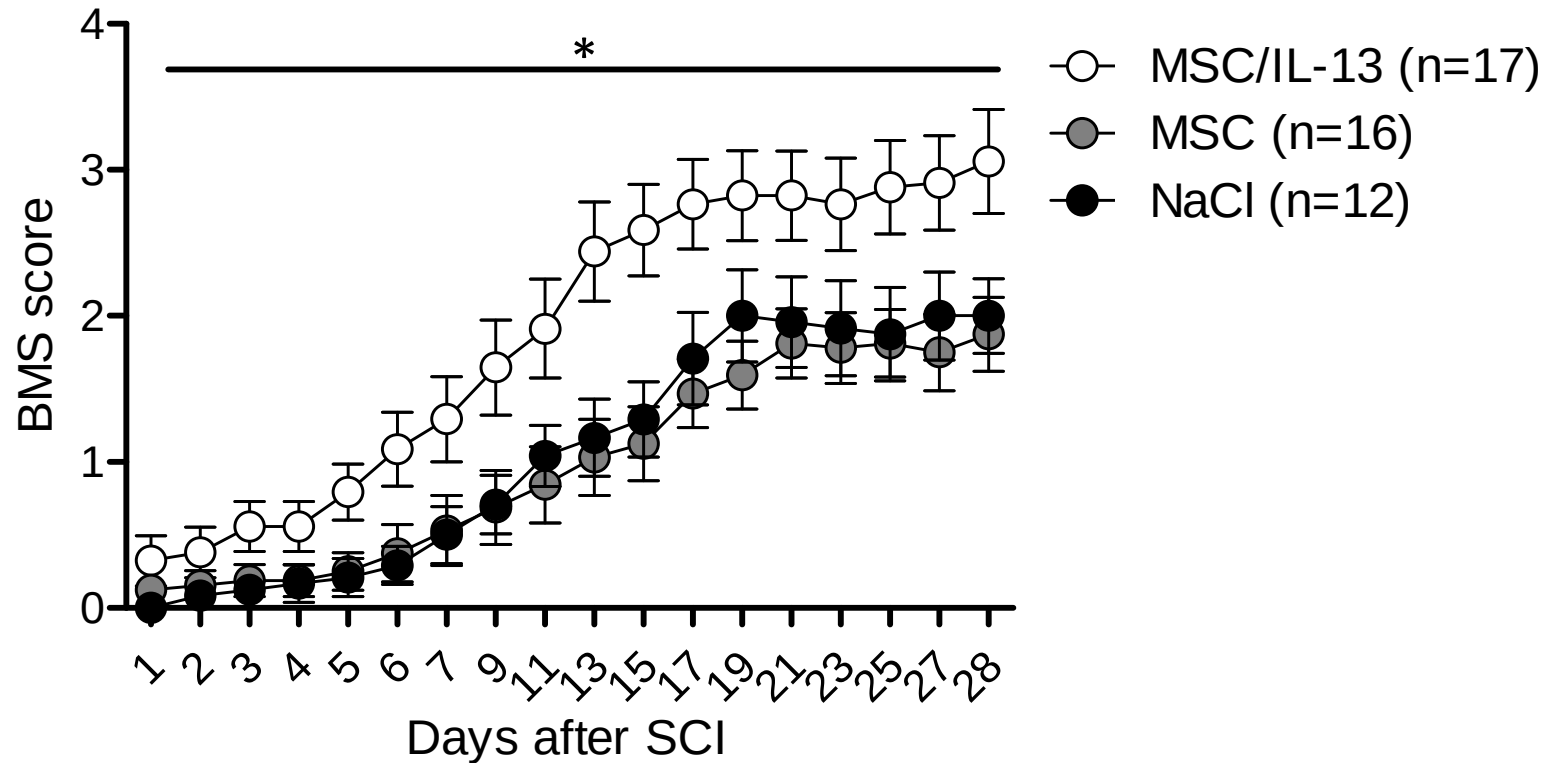
Transplantatie van IL13-producerende stamcellen in CPZ model (3)



**Bescherming tegen vernietigende microglia responsen en demyelinatie
gaat gepaard met het verschijnen van neuroprotectieve macrofagen**

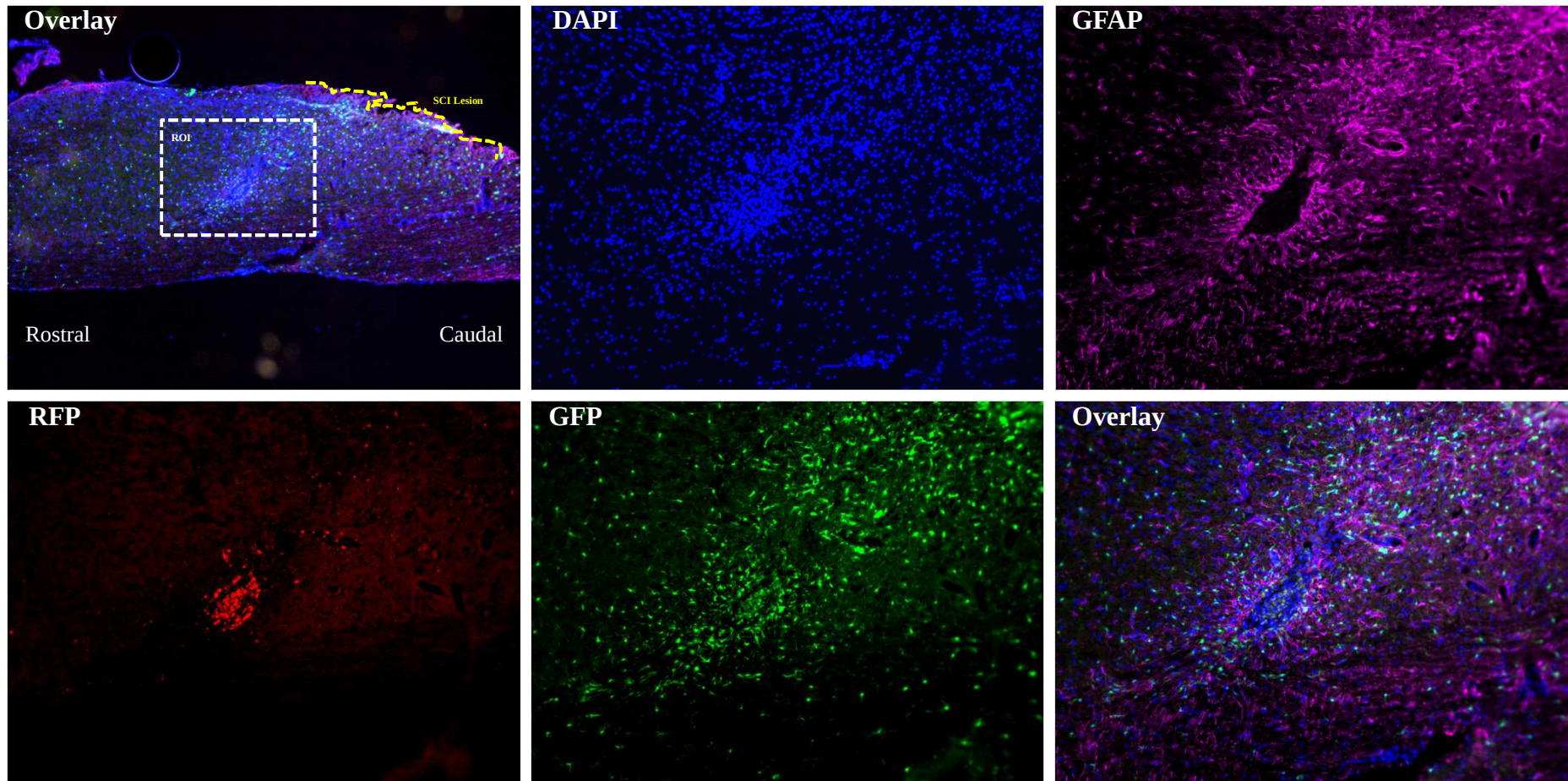


Transplantatie van IL13-producerende stamcellen in SCI model (1)



Ruggermergtrauma op T8 – Stamcelimplantatie in acute fase

Transplantatie van IL13-producerende stamcellen in SCI model (2)



Besluiten

- Stamceltherapie voor andere dan hematopoietische aandoeningen zit nog in een zeer vroeg onderzoeks / klinisch stadium ...
- Alhoewel veelbelovende preklinische resultaten, bestaat er momenteel geen overtuigend bewijs dat stamceltransplantatie beter, of zelfs maar even goed, is dan bestaande behandelingsmethoden voor ruggenmergtrauma ...
- Gerichte immunomodulatie en bescherming tegen degeneratie is slechts een eerste stap in een succesvolle behandeling van ruggenmergtrauma ...
- Stamceltherapie voor ruggenmergtrauma zal een plaats vinden in geneeskunde, maar het zal niet de eenvoudig te commercialiseren stamceltherapie zijn die ook de grootste efficaciteit zal bieden ...



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