

# The patient's own bone marrow-derived stromal cells

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## **7.2. Summary: the patient's own bone marrow-derived stromal cells as disease modifier in (neuro)degenerative disorders**

Neurodegenerative disorders share the final degenerative pathway, the cell death-induced secondary inflammation with progressive apoptosis and/or necrosis, irrespective of their aetiology. In two preclinical models for acute neurodegeneration (balloon-compressed and drop weight impact SCI models) and in two preclinical models for chronic neurodegeneration (ALS-like FUS 1-358 and SOD1-G93-A mutation), a GMP produced negative selected human bone marrow derived stem cell preparation (bm-SCs; Neuro-Cells) was tested for safety and efficacy.

After double-blind interventions with this preparation, with placebo, or with (non)steroidal anti-inflammatory drugs (methylprednisolone, riluzole, celecoxib), clinical, histological and histochemical findings (serum/spinal cytokines and markers for spinal microglial activation inclusive) evidenced the cell-to-cell action of bm-SCs in both otherwise healthy and immune-deficient tSCI-rats, as well as in wild-type and FUS/SOD1-transgenic ALS-like and FUS-transgenic FTLT-like mice. All studies yielded significantly better results in bm-SC-treated animals as compared to the animals treated with placebo and/or NSAIDs. In SCI-lesioned rats, bm-SCs led to faster motor recovery, less apoptotic cells and less astrocytes in the lesion as compared to vehicle and methylprednisolone. In ALS-like mice, bm-SCs led to less motor impairment, less muscle atrophy and a decreased loss of motor neurons in the spinal cord as compared to vehicle, riluzole and celecoxib treated animals. In the FUS-tg FTLT-like mice, after interventions with bm-SCs (Neuro-Cells), behavioural and molecular abnormalities of FUS-tg mice were also found reduced to a greater extent as compared to the interventions with riluzole and/or celecoxib.

The multi-pathway hypothesis of the action of bmSCs, presumably through extracellular vesicles (EVs) as messaging carriers of RNA, DNA, proteins and lipids, rather than influencing a single inflammatory pathway, could be justified by the established differences of serum and spinal tissue levels of cytokines and other chemokines. The mode of action of bm-SCs is hypothesized to be associated with its dedicated adjusting of the pro-apoptotic glycogen synthase kinase-3 $\beta$  level towards an anti-apoptotic level whereas their multi-pathway hypothesis seems to be confirmed by the decreased levels of the pro-inflammatory interleukin (IL)-1 $\beta$  and tumor necrosing factor (TNF) as well as the level of the marker of activated microglia, ionized calcium binding adapter (Iba)-1 level. With the results presented, the next phase, translating the results into humans seems justified.

### **7.3. Samenvatting: patiënt's eigen beenmerg stamcellen om (neuro)degeneratieve aandoeningen aan te pakken**

Hoewel de oorzaken van de diverse neurodegeneratieve aandoeningen niet altijd bekend zijn, delen deze aandoeningen wel dezelfde pathofysiologie. De initiële celdood en necrose in het centrale zenuwstelsel zijn verantwoordelijk voor het activeren van de secundaire ontstekingscascades.

In preklinische diermodellen voor acute (balloncompressie en slaggewicht-geïnduceerde ruggenmergletsels) en chronische (FUS-1-358 en SOD1-G93-A mutatie) neurodegeneratieve processen, is een uit menselijk beenmerg afkomstig stamcel preparaat (bm-SCs, Neuro-Cells) getest op veiligheid en werkzaamheid.

Dit stamcel product is onder GMP-condities en met negatieve selectie tot stand gekomen. In een dubbelblinde studieopzet is het stamcel preparaat vergeleken met een niet-werkzame placebo, danwel ontstekingsremmers: (N)SAIDS zoals methyl-prednisolon, riluzole en celecoxib.

In vergelijking tot placebo- en methylprednisolon-behandelde dieren, verbeterde de achterpoot functie van de met stamcellen behandelde dwarslaesie dieren significant sneller, en was er sprake van minder celdood en een lagere concentratie aan ontstekingscellen (astrocyten) in het beschadigde weefsel.

Van de ALS-achtige dieren vertoonden de dieren behandeld met stamcellen significant minder uitval van de spierfuncties, hadden deze dieren minder spieratrofie en was er sprake van een significant hoger aantal intacte motorneuronen in het spinale weefsel in vergelijking tot de dieren behandeld met placebo, riluzole of celecoxib. Tenslotte bleken de met stamcellen-behandelde FTLD-achtige muizen significant beschermd voor de normaal in deze dieren optredende verhoging van de IL-1 $\beta$  en GSK-3 $\beta$  concentraties. Ook bleken de hier optredende gedragsafwijkingen duidelijk afgenomen, veel meer dan na interventies met riluzole en/of celecoxib.

De resultaten van de serum cytokinen en de western-blot weefsel preparaten in de bm-SC-behandelde proefdieren maken het aannemelijk dat de stamcellen multi-taskers waren, die meerdere processen tegelijkertijd beïnvloeden, hierbij gebruik makend van extracellulaire vesicles als communicatoren voor de interactie. Op basis van ons onderzoek mag ervan uitgegaan worden dat bm-SCs (Neuro-Cells) in preklinische neurodegeneratieve ziekteprocessen vooral werkzaam is door het onderdrukken respectievelijk voorkomen van de in deze ziekten aanwezige progressieve activatie van het GSK-3 $\beta$ , die gepaard gaat met de aantasting van de verbindingen tussen het endoplasmatisch reticulum en de mitochondria, waardoor een tekort aan ATP met necrose optreedt.

Op grond van de door ons verkregen preklinische resultaten lijkt het gerechtvaardigd de vastgestelde gunstige effecten van bm-SCs te vertalen naar een mogelijk ziekte-modificerende behandeling voor humane (neuro)degeneratieve aandoeningen.