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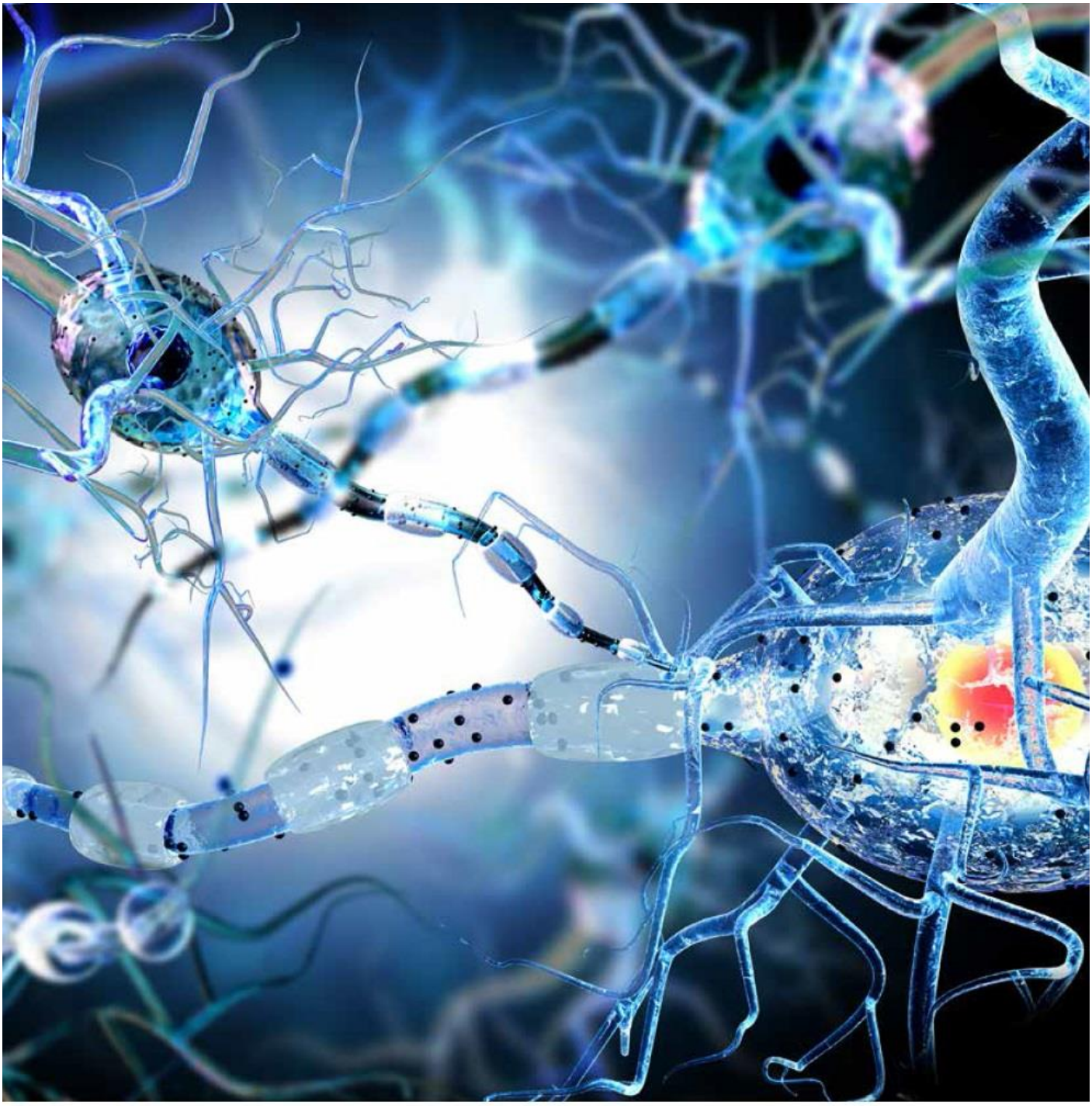
ABSTRACT BOOK



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Poster Board #01

A Novel Perspective on the Growing Global Burden of Multiple Sclerosis

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Background:
Affecting over 2.5 million globally, Multiple Sclerosis (MS) is one of the most disabling diseases. Specific infections and antibiotics have been attributed as the causative factors but otherwise it is an inflammatory condition whose aetiology seems elusive.
The Unified Theory of a Continuum of Diseases proposes that when acute inflammatory diseases are suppressed with strong drugs repeatedly, the immune system loses the ability to defend itself through efficient acute inflammation. Instead, it enters a state of low grade chronic inflammation which eventually triggers the chronic disease that the person is predisposed to genetically. This means that a clear shift in the immune response occurs from efficient acute to low grade chronic inflammation in these people.

Objectives:
To investigate if there is decrease in acute inflammatory diseases after onset of MS and if it may be attributable to suppression with drugs.

Methods:
100 consenting MS patients' past medical history was studied for:
Recurrent acute infectious/inflammatory diseases
Mode of treatment of these diseases
History of fevers/acute infections before and after onset of MS - along with the respective highest temperatures

Results:
80 persons - history of acute infectious diseases, repeatedly treated with antibiotics
12 persons - history of recurrent acute infectious diseases, without any abuse of antibiotics
2 persons - no clarity
After onset of MS:
6 persons - high fevers of 40° C (a sign of efficient acute inflammation)
53 persons - occasional fevers but low grade.
40 persons - no fevers

Conclusion:
This study provides basis to further investigate the correlation between indiscriminate suppression of acute inflammatory states with drugs and development of chronic inflammatory diseases such as MS.

Poster Board #02

Three-Dimensional Lesion Phenotyping and Physiologic Characterization Inform on Remyelination Capacity in Multiple Sclerosis

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Background:
Disease characterization in multiple sclerosis (MS) is currently based on two-dimensional forced-perspective MRI data. Such views fail to reveal the complexity of lesion shape and surface texture along with their relationships to the magnitude of injury within and around lesions, the extent of metabolic alterations, and potential for self-remyelination and recovery.

Objective:
To utilize a novel three-dimensional (3D) lesion phenotyping approach coupled with physiologic measures to study the impact of metabolic and physiologic profiles within and around lesions and associations with lesion shape and surface texture.

Methods:
Focal lesions were isolated and edited in 3D from 3T T_2-FLAIR images using geodesic active contouring. Physiological metrics were studied within lesions and surrounding tissue in concentric 3mm layers exact to the 3D lesion shape. A dual-echo calibrated functional MRI sequence permitted measurement of cerebral blood flow (CBF), blood-oxygen level dependent (BOLD) signal, and cerebral metabolic rate of oxygen ($CMRO_2$). BOLD slope was determined by measuring signal changes within a lesion to the surrounding perimeters. White-matter integrity was measured using diffusion kurtosis imaging. Associations between these metrics and 3D lesion shape and surface characteristic data were determined.

Results:
A total of 109 lesions were studied from 23 MS patients (17 female; median age: 50.6 years, range: 30.0-61.4) with median disease duration of 11.3 years (range: 1.2-30.8). Metabolically active lesions with positive BOLD slopes had higher $CMRO_2$ (p0.0005) and CBF (p0.03) compared to inactive lesions. Mean, axial, and radial kurtosis were significantly higher in metabolically active lesions (p0.0005). Lesions with more dynamic surface textures and less complex shapes were associated with higher metabolic and myelin repair-related signatures within identified lesions and surrounding tissue (p0.0001).

Conclusion:
3D phenotyping informs on metabolic activity, lesion age, and risk for disease reactivation. Our findings also provide a platform for disease surveillance and outcome quantification involving emerging myelin repair therapeutics.

Poster Board #03

The Role of RNA Editing in Immune Mediated Autoimmune Encephalomyelitis (EAE) Progression with Implications in Multiple Sclerosis (MS) Pathogenesis

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Introduction:
Combined environmental, genetic and epigenetic factors, including RNA-editing, are expected to be crucial in Multiple Sclerosis (MS) pathogenesis. RNA editing, a site-specific modification is a co-transcriptional modification of pre-mRNA performed by enzymes: ADARs, converting adenosine-to-inosine (A-to-I) and APOBECs converting cytidine-to-uracil (C-to-U) by deamination. RNA-editing allows multiple protein products from a single gene. Confirmed APOBEC1 expression lead the hypothesis that microglia express APOBEC1 and its targets.

Methods:
We utilized APOBEC1$^{-/-}$ transgenic animals (KO) to address whether depletion of APOBEC1-mediated editing affects EAE progression, a suitable model for inflammation/demyelination phenotypes. Our objective is to systematically identify and elucidate editing events associated with disease mechanisms.

Results:
Wt and APOBEC1 KO mice with EAE, clearly indicated differences in disease severity, based on the development of ascending flaccid hind limb paralysis. Animals exhibited a moderate to severe acute phase of EAE without mortality; mean Maximal Score of KO was significantly higher compared to wt (4.68 ± 0.16 versus 2.43 ± 0.42; P 0.01). Mean day of Disease Onset was 13.63 ± 0.18 days for KO while 14.50 ± 0.26 days for wt (P 0.05). RNA Sequencing data were utilized to directly compare genomes leading to accurate detection of microglial RNA: DNA editing differences. Comparing hyper-/hypo-edited transcripts generated MS-related editomes which are enriched for Endoplasmic Reticulum (ER) stress and lysosomal signaling pathways. Selected differentially edited and expressed transcripts have been validated and are currently examined in human brain autopsy material. Such a study will generate novel therapeutic targets across the breadth of neurodegenerative disorders.

Poster Board #04

Neuralized Mesenchymal Stem Cells: A Novel Cellular Therapy Paradigm for the Treatment of Multiple Sclerosis

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Background:
In the last few years several preclinical studies indicated the therapeutic potential of MSC in MS. Moreover, few clinical studies showed positive results with the use of MSC in MS. The mechanisms of action of MSC in the MS disease model seem to be mainly mediated through immunomodulation and neuroprotection. The possibility of tissue regeneration with the use of MSC is still debatable. Theoretically the “neuralization“ of MSC could provide additional benefits for clinical applications in MS and potentially stronger neuro-regenerative and remyelinating effects .

Methods:
MSC were isolated from the bone marrow (BM) of MS patients. The MSC were cultured in a medium containing EGF, bFGF and B27 supplement to generate NMSC. The NMSC were characterized using FACS. The neural differentiation of the NMSC was achieved by a novel culturing method using cerebrospinal fluid (CSF). The immunomodulatory effects of NMSC were tested using a lymphocytes suppression assay in vitro. The neurotrophic effects were evaluated by measuring the quantities of secreted growth factors. For in vivo studies, we used the chronic EAE model induced in female C57BL/6 mice induced with MOG_{35-55} peptide. On days 8-10 after immunization the NMSC were injected intraventricularly. The animals were scored daily for neurological symptoms according to the EAE clinical severity scale. Histopathological stains were used to evaluate inflammation and axonal loss.

Results:
NMSC (floating spherical shape cell structures) were generated successfully from all of the batches of naïve MSC. The spheres were stained positively for the neurosphere markers Nestin and PS-Ncam (>90%) while were negative for the mesenchymal markers CD90 and CD105 (<5%). The NMSC lost their ability to differentiate to mesodermal tissues (adipocytes and osteocytes). The generated MSC-NPs were found to induce a dose-dependent suppression of lymphocytes proliferation. NMSC were differentiated successfully to neurons (MAP2 marker, ~70% of cells), astrocytes (GFAP, marker, ~20% of the cells) and oligodendrocytes (CNPase marker, ~10% of the cells). Moreover, the NMSC and differentiated NMSC secreted higher levels of neurotrophic factors (BDNF, NGF, CNTF, GDNF) compared to naïve MSC. NMSC attenuated cEAE severity after transplantation; differentiated NMSC induced significantly better clinical effects. The mortality in NMSC treated animals (n=8), was 0% and the mean maximal EAE score 1.75 vs. 33.3% mortality and 3.33 mean maximal score in non-treated animals (n=10). Mice treated with differentiated NMSC (n=12) showed 0% mortality and a mean maximal EAE score of 0.6 (significantly better than the 1.75 of MSC-NPs treated mice and the 3.33 of the untreated animals).

Conclusions:
The generation and differentiation of NMSC from naïve MSC seems to improve their efficacy by increasing the neuroprotective effects, while preserving their immunomodulatory properties. Such “neuralized” MSC could be better candidates for future cell therapies than regular unmodified MSC.

Poster Board #05

Glucocorticoids Attenuate Experimental Autoimmune Encephalomyelitis Via Increasing G-MDSC Proportion

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Background:
Previous studies have shown that myeloid-derived suppressor cells (MDSCs) abundantly accumulate within peripheral blood and spleen of mice with experimental autoimmune encephalomyelitis at disease onset . Glucocorticoids are the main drugs treating acute episode and relapse of multiple sclerosis (MS). However, little is known how glucocorticoids affect MDSCs in EAE models.

Objective:
To investigate the influence of glucocorticoids on MDSCs in EAE model.

Methods:
C57BL/6 mice were immunized with 200□g MOG35-55 emulsified with Complete Freund´s Adjuvant (CFA). Pertussis toxin (PT) was intraperitoneally injected at 300ng/per mouse at day 0 and 2 post immunization. Furthermore, EAE mice were treated by injecting high-dose methylprednisolone intravenously everyday? Then percentages of MDSCs and regulatory (Treg) cells in PBMC and splenocytes of EAE mice were measured by flow cytometry, and suppressive activity of MDSCs from EAE mice with or without glucocorticoid treatment was measured by T cell proliferation assay.

Results:
Compared with naive mice, the percentages of MDSCs in PBMC and splenocytes of EAE mice significantly increased at disease onset. High-dose methylprednisolone treatment could relieve disease progress. Unexpectedly, methylprednisolone-treated EAE mice had a comparable MDSC level in PBMC compared to Non-treated counterparts, but the ratio of G-MDSCs in MDSCs was significantly elevated. In addition, glucocorticoids did not change the percentages of splenic MDSCs and their subpopulations of EAE mice. Furthermore, splenic MDSCs had comparable activity in suppressing T-cell proliferation no matter with or without glucocorticoid treatment, and M-MDSCs showed more potent suppressive activity than G-MDSCs. Unlike previous studies, Glucocorticoid did not change the percentages of Treg in CD4+ T cells in PBMC and splenocytes of EAE mice.

Conclusions:
The frequency of MDSCs in PBMC and the splenocytes of EAE mice significantly increase, Glucocorticoid treatment attenuates disease development via raising the ratio of G-MDSCs in total MDSCs, but not alter the suppressive activity for MDSCs.

Poster Board #06

Intrathecal Delivery of Autologous Mesenchymal Stem Cells in Patients with Amyotrophic Lateral Sclerosis in Greece: A challenge for the Future

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Background:
Amyotrophic lateral sclerosis (ALS) is a rare and devastating neurodegenerative disease affecting motor neurons and leading to tetraplegia, respiratory insufficiency and death within a few years. Available approved treatments for the disease do not alter significantly disease progression.

Objective:
To determine the safety and effectiveness of autologous mesenchymal stem cells (MSC) in patients with ALS and compare them to a control group of patients receiving standard care.

Methods:
Data was collected in a three-year period. Group A included forty-one (41) patients with definite ALS (19 with prominent bulbar symptoms). Baseline ALS functional rating scale (ALSFRS) was between 30-38/42. Male to female ratio: 1.2/1. All of them underwent a bone marrow biopsy to collect autologous MSCs which were then cultivated in a dedicated centre towards nerve cells. At a second appointment, these cells were infused intrathecally and the patients were followed clinically at one month, three months, and 6 months. 52% of the patients received a second infusion at three months and 23% a third infusion at six months. Group B included 41 patients with similar demographic characteristics receiving standard care.

Results:
In Group A, no deaths were observed in this time period. All of the side effects were self-limiting infusion reactions (headache, fever, etc.) and none of those was severe. Overall, the procedure was safe for all patients. Compared to Control Group B, 50% patients showed decrease in disease progression (at all three timepoints). The subgroup of patients receiving larger number of cells had more favourable results

Conclusion:
Autologous MSCs is a safe treatment method which offers some stabilization of a devastating neurological disease. There is of course dire need for effective treatments for this group of patients.