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IFN-γ/IL-27 axis induces PD-L1 expression in monocyte-derived dendritic cells and restores immune tolerance in CNS autoimmunity

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(*) indicates primary project advisor

(**) indicates another student who is declaring the same project as primary for SI

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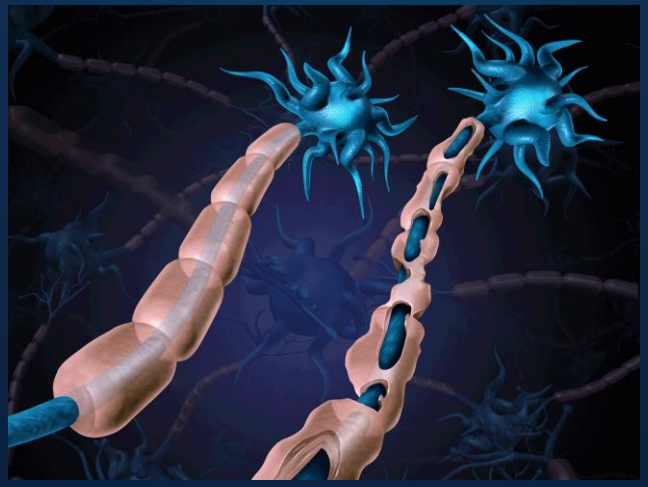
Introduction: Clinical Significance

- Multiple sclerosis (MS) is an autoimmune disease of the CNS involving inflammation and demyelination
- Presents with varying debilitating symptoms including fatigue, pain, tremor, and paralysis
- Affects over 100 per 100,000 people in North America



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Introduction: Background

- Therapies based on restoring Ag-specific immune tolerance induction have been a long-standing goal for treatment of autoimmune diseases
- Advantage of Ag-specific therapy
  - Selective suppression of a pathogenic immune response
  - Not impairing systemic immunity → avoid adverse effects of immunosuppression
- Previous studies of auto-Ag IV tolerance induction
  - Extensively studied in experimental autoimmune encephalomyelitis (EAE), an animal model of MS
  - Limited clinical trials demonstrated that it is safe and beneficial to a subset of MS patients
- Mechanisms of IV tolerance induction are incompletely understood, which limits the development of better approaches and their clinical application

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Objectives & Hypothesis

- Research Question
  - How does the IFN-γ/IL-27/PD-L1 axis affect mice with an animal model of multiple sclerosis?
- Hypothesis
  - In mice with an animal model of multiple sclerosis, the IFN-γ/IL-27/PD-L1 axis leads to apoptosis of pathogenic CD4+ T cells, resulting in amelioration of disease.

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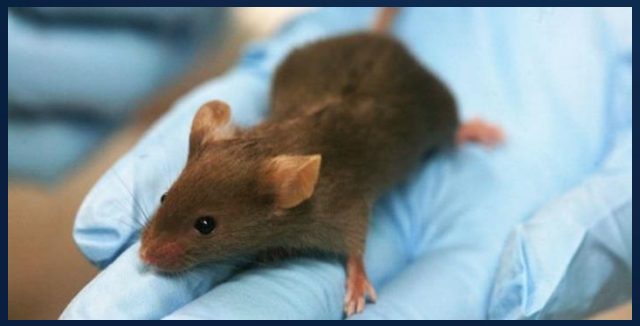
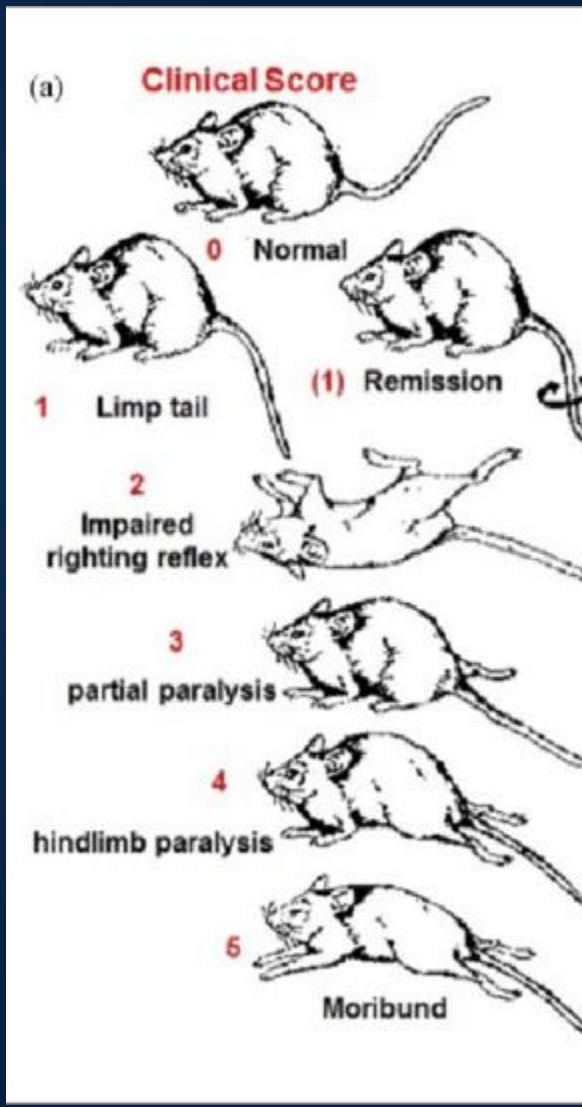
Approach & Results

- Experimental protocols using mice (n=10/group per experiment) were approved by IACUC of TJU
- EAE
  - Injection of MOG peptide, heat-killed *Mycobacterium tuberculosis*, pertussis toxin
  - Daily clinical assessment
- PD-L1, PD-L2, IFN-γ blockade via MAb injection
- IV Tolerance Induction after onset of clinical disease
  - Injections of MOG every third day, three times
  - Control mice received vehicle only
- Isolation of cells from spleen and CNS
- Analysis techniques: flow cytometry, ELISA, qPCR





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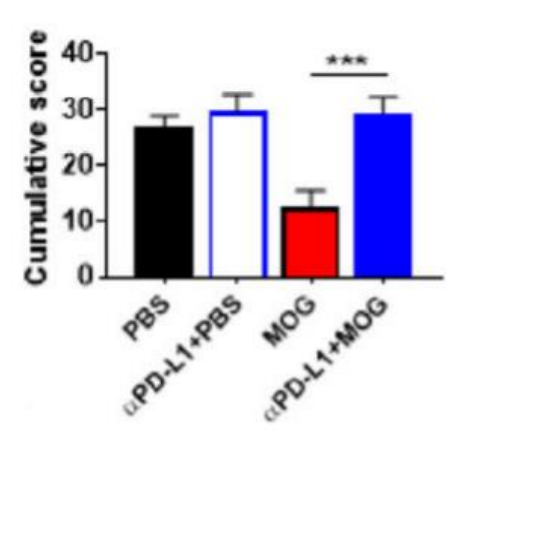
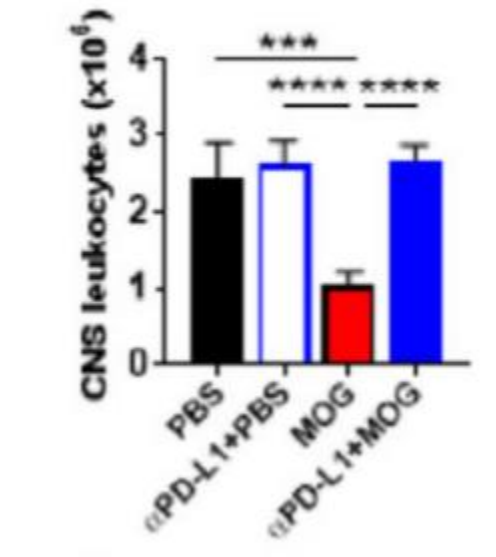
Approach & Results

Intravenous Tolerance Induction in EAE Is Dependent on Programmed Death Ligand 1 (PD-L1)





Analyses between two groups were carried out by Student's t-test and between four groups by one-way ANOVA with Bonferroni post-test. EAE experiments were analyzed by two-way ANOVA with Bonferroni's multiple comparison. Values of ** $P < 0.001$, *** $P < 0.0001$, and **** $P < 0.00001$ were considered significant.

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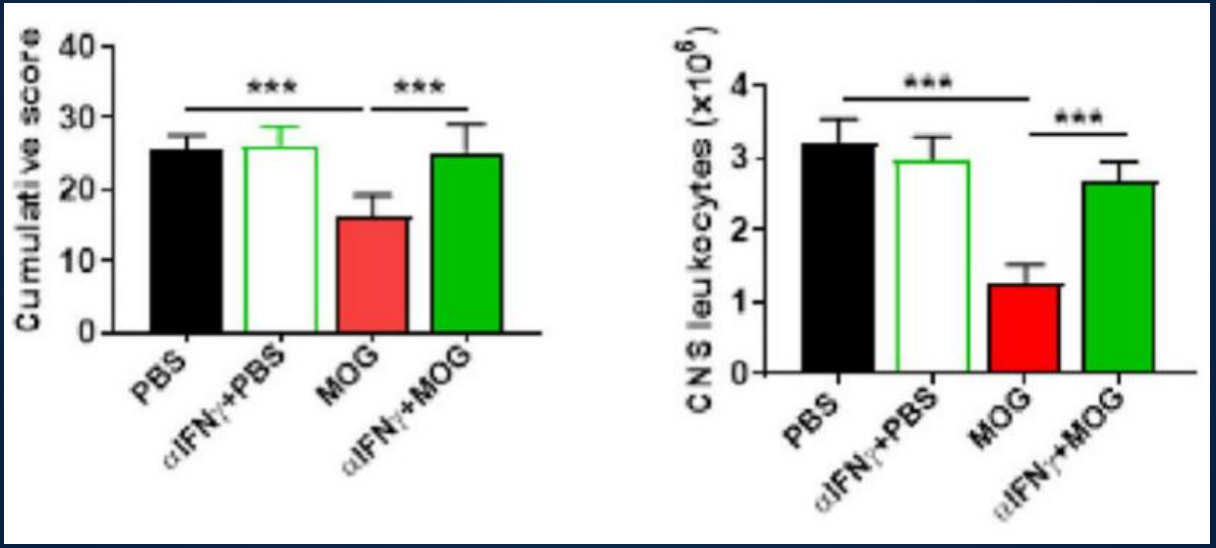
Approach & Results

Interferon-γ Secreted by CD4+ T Cells Is Necessary for EAE Suppression Upon MOG/IV Treatment



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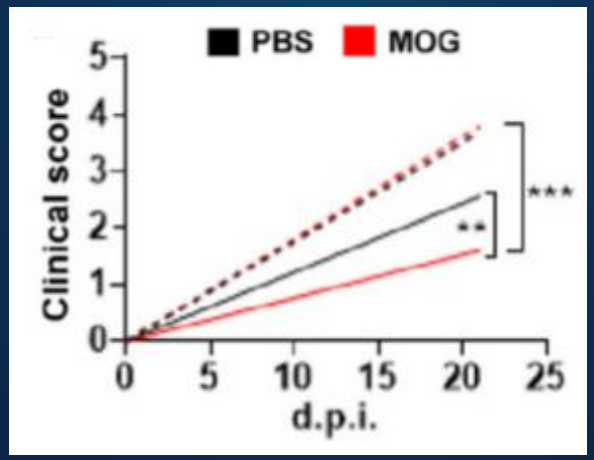
Approach & Results

Interleukin-27 Induces PD-L1 Expression in Monocyte-Derived Dendritic Cells and Improves Disease Outcomes



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Conclusions

- IV Auto-Ag injected into mice with clinical EAE → IFN-γ → IL-27 → PD-L1 → apoptosis/anergy of pathogenic CD4+ T cells → disease amelioration
- Depletion of autoreactive is a well-known mechanism of tolerance, but our study defines a pathway between molecular and cellular factors that leads to this development
- Sheds light on this signaling axis and the use of immune tolerance as a potential therapeutic in people with MS

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Future Directions

- Additional molecules may be involved in this pathway, such as IL-10
- Upregulation of TGF-β has also been noted, but its significance has not been explored
- This regulatory pathway is relevant in other contexts
- Explore use of immune tolerance in other autoimmune diseases

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