



## Commentary

# Antigen-specific immunotherapy for MOG antibody-associated diseases

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Antibodies targeting myelin oligodendrocyte glycoprotein (MOG), a membrane-embedded surface protein of the central nervous system (CNS) myelin sheath, have been consistently found in the sera of children and adults suffering from acquired inflammatory demyelinating disorders of the CNS. The clinical spectrum associated with MOG antibodies includes acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis and brainstem encephalitis. Serum MOG antibodies can be transient or persistent in patients. The latter is associated with an increased risk of developing a relapsing disease course [1,2] and thus attack-related and accumulating disabilities.

Disease-modifying therapies (DMTs) in patients with persisting serum MOG antibodies remain challenging. DMTs such as interferon beta or glatiramer acetate, which are regularly used in patients with multiple sclerosis (MS), are usually not effective [3,4]. Interestingly, 85% of MOG antibody-positive patients also continued to relapse while on rituximab [3], an antibody which depletes CD20<sup>+</sup> B cells and rapidly and efficiently reduces relapse rates in relapsing-remitting MS [5]. Current preventive treatment strategies for MOG antibody-associated diseases include the prolonged tapering of steroids combined with oral immunosuppressants, IVIG or anti-CD20 antibodies. Of note, some patients have to remain on long-term steroid or IVIG maintenance in order to efficiently suppress relapses. Thus, novel treatment strategies are urgently required.

In this article of *EBioMedicine*, Fovet and Stimmer et al. ameliorated recombinant human MOG (rh MOG1-125)-induced experimental autoimmune encephalomyelitis (EAE) in macaques, a preclinical non-human primate (NHP) model with demyelinating MOG-specific antibodies likely by inducing tolerogenic dendritic cells (tolDC) [6]. The authors follow up on previous work [7] and fused MOG to an antibody which targets the DC asialoglycoprotein receptor (DC-ASGPR), a C-type lectin receptor expressed on myeloid DC in humans and NHP. The DC-ASGPR-mediated uptake

of MOG elicited an antigen-specific regulatory T cell (Tregs) response, which efficiently suppressed MOG-induced CNS autoimmunity in a small cohort of macaques undergoing preventive or therapeutic treatment regimens.

The intradermally injected and DC-ASGPR targeted MOG was preferentially taken up by CD163<sup>+</sup> dermal cells, whereas control MOG was phagocytosed by CD1a<sup>+</sup> Langerhans cells. The precise origin of the CD163<sup>+</sup> dermal cells, which phagocytose the DC-ASGPR targeted MOG, will be of relevance to better tailor antigen-presenting cells for functional Treg expansion. Interestingly, in a recent publication CD163 was proposed as a surface marker for circulating IL-10-producing human DC [8]. In addition, the mechanisms by which DC-ASGPR signalling might induce IL-10 in human DC were also recently described [9].

Repetitive intradermal injections of DC-ASGPR-targeted MOG increased the frequency of CD4<sup>+</sup> CD25<sup>+</sup> FoxP3<sup>+</sup> CD39<sup>+</sup> Tregs but did not induce a MOG-specific antibody response in macaques. Also, if given after immunization with MOG/IFA, DC-ASGPR-targeted MOG did not impact MOG-specific serum antibody concentrations but increased serum TGF-beta levels, a cytokine well known for its immunosuppressive capabilities.

In summary, Fovet and Stimmer et al. demonstrate the safety and efficacy of an antigen-specific immunotherapy in a NHP model of MOG-induced autoimmune CNS demyelination lending perspective to antigen-specific therapies in selected human autoimmune diseases.

### Author's contribution

Stefan Nessler wrote the commentary.

### Declaration of Competing Interest

The author declares no conflict of interest.

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## References

- [1] Baumann M, Hennes EM, Schanda K, Karenfort M, Kornek B, Seidl R, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): extending the spectrum of MOG antibody positive diseases. *Mult Scler* 2016;22(14):1821–9.
- [2] Jurynczyk M, Messina S, Woodhall MR, Raza N, Everett R, Roca-Fernandez A, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain* 2017;140(12):3128–38.
- [3] Hacoen Y, Wong YY, Lechner C, Jurynczyk M, Wright S, Konuskan B, et al. Disease course and treatment responses in children with relapsing myelin oligodendrocyte glycoprotein antibody-associated disease. *JAMA Neurol* 2018;75(4):478–87.
- [4] Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinflammation* 2016;13(1):280.
- [5] Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358(7):676–88.
- [6] Fovet CM, Stimmer L, Contreras V, Horellou P, Hubert A, Seddiki N, et al. Intradermal vaccination prevents anti-MOG autoimmune encephalomyelitis in macaques. *EBioMedicine* 2019. <https://doi.org/10.1016/j.ebiom.2019.08.052>.
- [7] Li D, Romain G, Flamar AL, Duluc D, Dullaers M, Li XH, et al. Targeting self- and foreign antigens to dendritic cells via DC-ASGPR generates IL-10-producing suppressive CD4+ T cells. *J Exp Med* 2012;209(1):109–21.
- [8] Comi M, Avancini D, Santoni de Sio F, Villa M, Uyeda MJ, Floris M, et al. Coexpression of CD163 and CD141 identifies human circulating IL-10-producing dendritic cells (DC-10). *Cell Mol Immunol* 2019. <https://doi.org/10.1038/s41423-019-0218-0>.
- [9] Gu C, Wang L, Zurawski S, Oh S. Signaling cascade through DC-ASGPR induces transcriptionally active CREB for IL-10 induction and immune regulation. *J Immunol* 2019;203(2):389–99.