

Blockage of BMP-2/4 Signaling by Neutralizing Ab or Small Molecule Induces Remyelination and Oligodendrocyte Differentiation in Cuprizone Model of Demyelination

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BACKGROUND

- Oligodendrocyte regeneration and myelin repair are important goals in multiple sclerosis.
- Bone morphogenetic factors (BMPs) are factors that block oligodendrogenesis and remyelination.
- Increased BMP expression was observed in animal models of demyelination induced by cuprizone, ethidium bromide, or lysolecithin.

OBJECTIVE

To examine the effect of BMP-2 blockade, by anti-BMP-2/4 neutralizing Ab or by a BMP-2- inhibiting small molecule (SM) on remyelination and oligodendrocytes differentiation in the cuprizone model.

METHODS

- We used high throughput screening (HTS) for sorting of SMs that block BMP-2- induced-alkaline phosphatase (ALP) production in ATDC5 chondrogenic cells. SM1, from Maybridge library, was found to have an optimal IC50 (2.6μM), with an ameliorating effect in experimental autoimmune encephalomyelitis (EAE), similarly to the anti- BMP-2/4 neutralizing Ab.

SM1 discovery and its effect in relapsing EAE

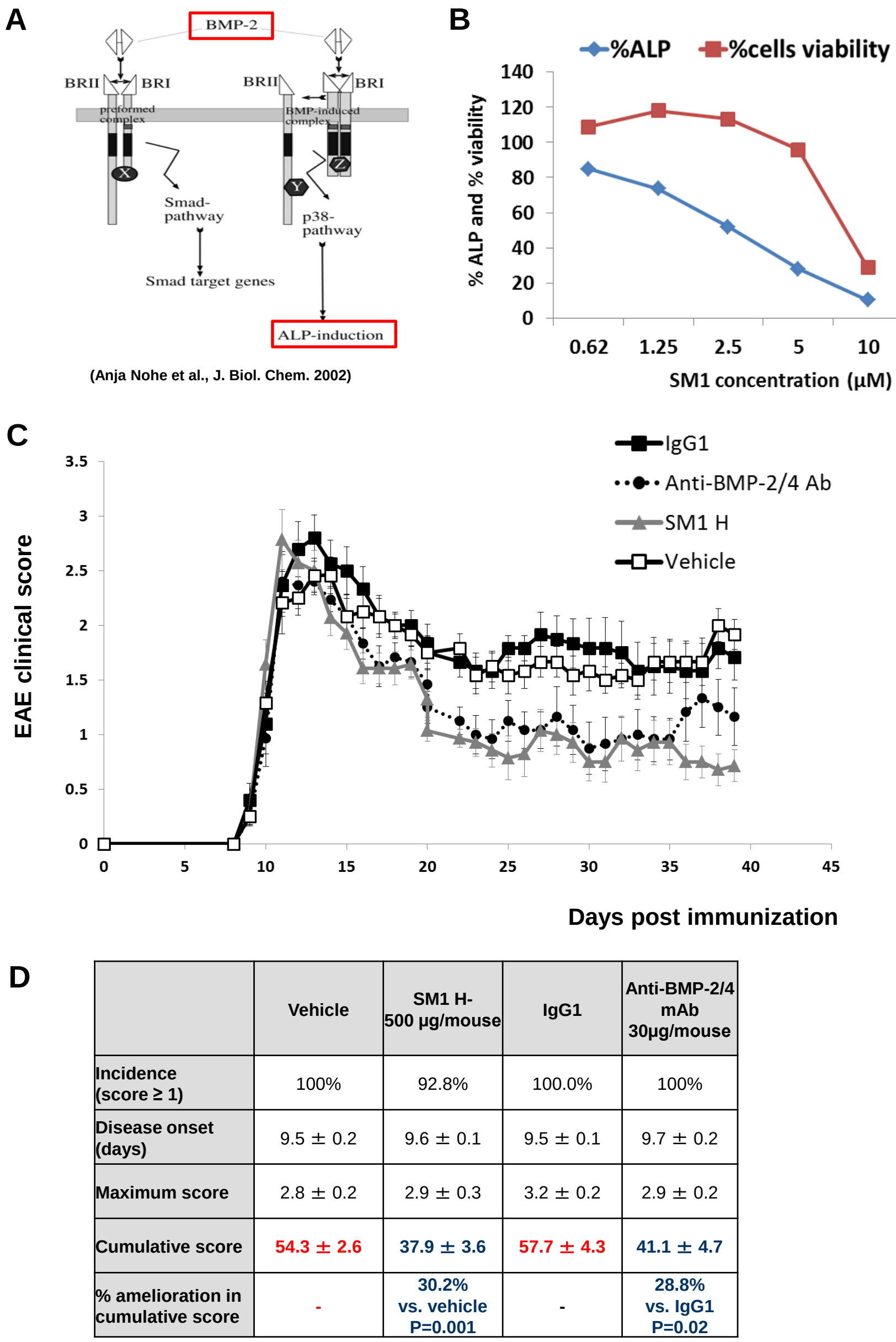
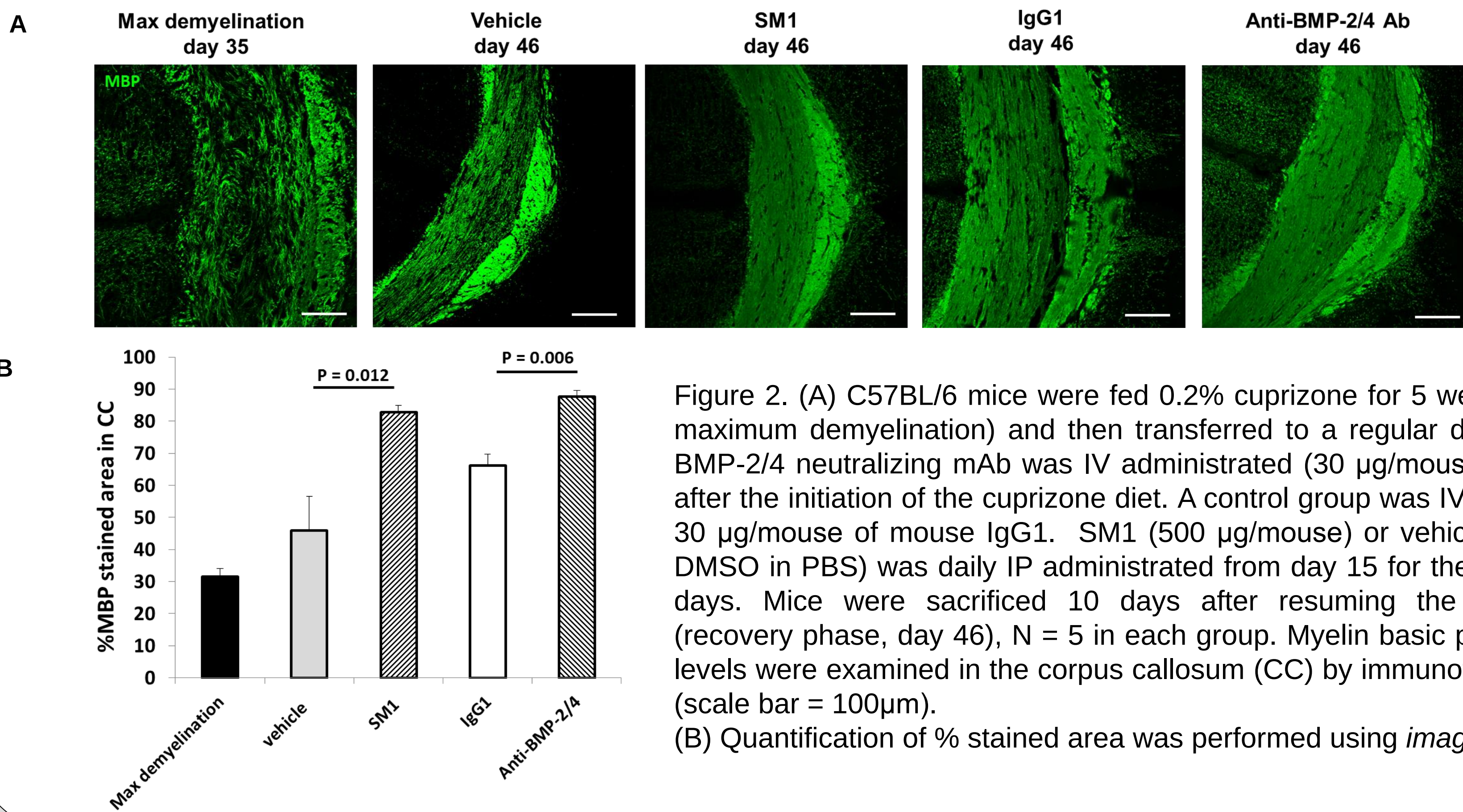


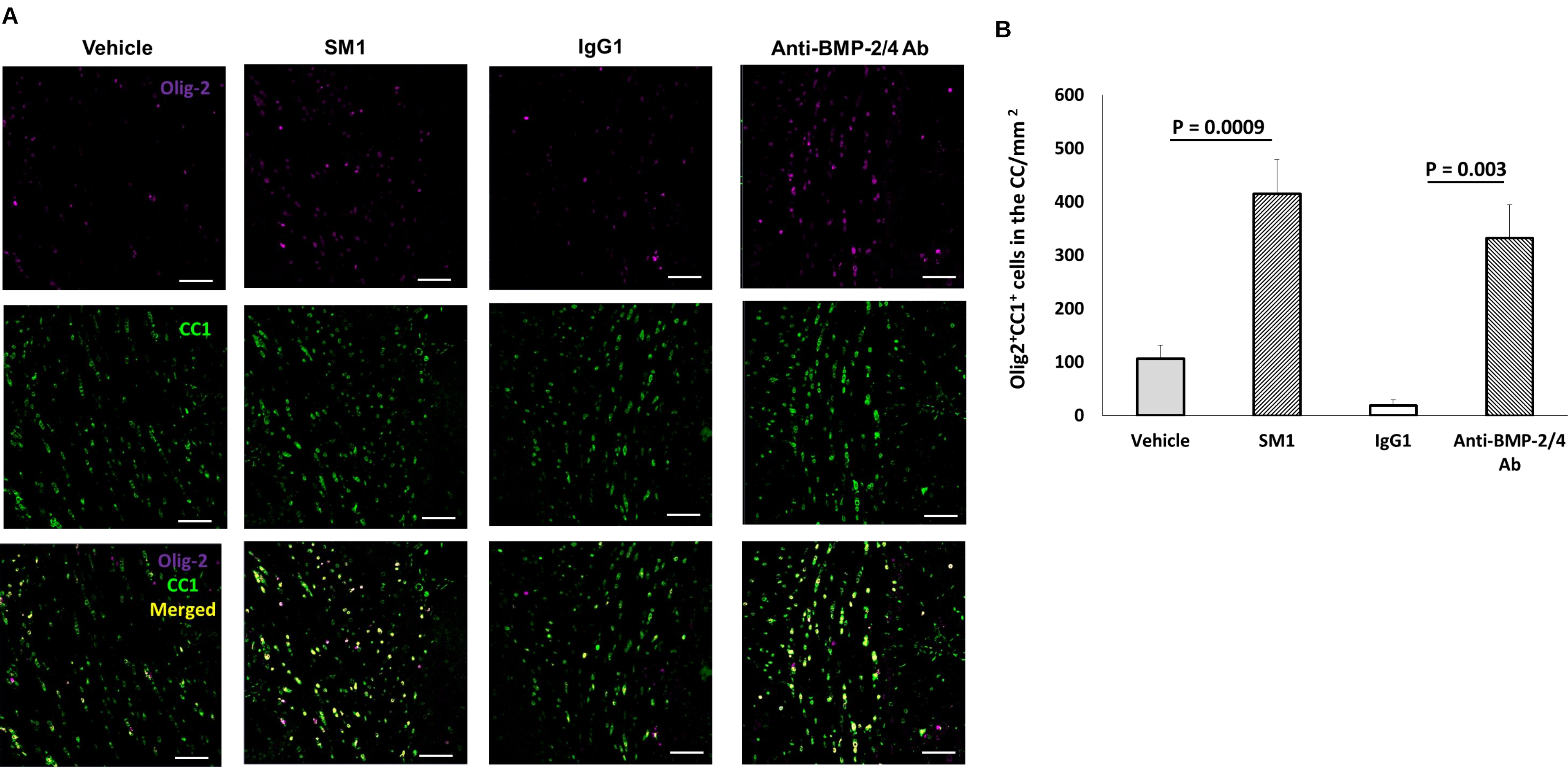
Figure 1. (A) Sorting for SMs that block BMP-2 signaling was based on the principle of BMP-2 neutralization bioassay. rhBMP-2 is known to induce alkaline phosphatase (ALP) production in ATDC5 cells, chondrogenic cell line, via p38- pathway. (B) Following screening of 7600 Maybridge compounds, we received 96 potential hits, i.e. % inhibition of ALP production by BMP-2 stimulation was higher than 25% and toxicity level was lower than 20%. These hits were re-examined in a dose-dependent manner for IC50 determination. SM1 demonstrated the top IC50 value (2.6μM). (C) Relapsing EAE (R-EAE)- induced mice were daily IP administrated with either SM1 (500 μg/mouse) or vehicle alone (5% DMSO in PBS) starting from day 9 post immunization for 30 following days. R-EAE mice were also IV administrated with anti- BMP-2/4 neutralizing mAb (R&D systems) or the corresponding IC, IgG1, on day 9 post-immunization (30 μg/mouse). The table presented in (D) summarizes the clinical characteristics of R-EAE mice. N=14 in each group.

RESULTS

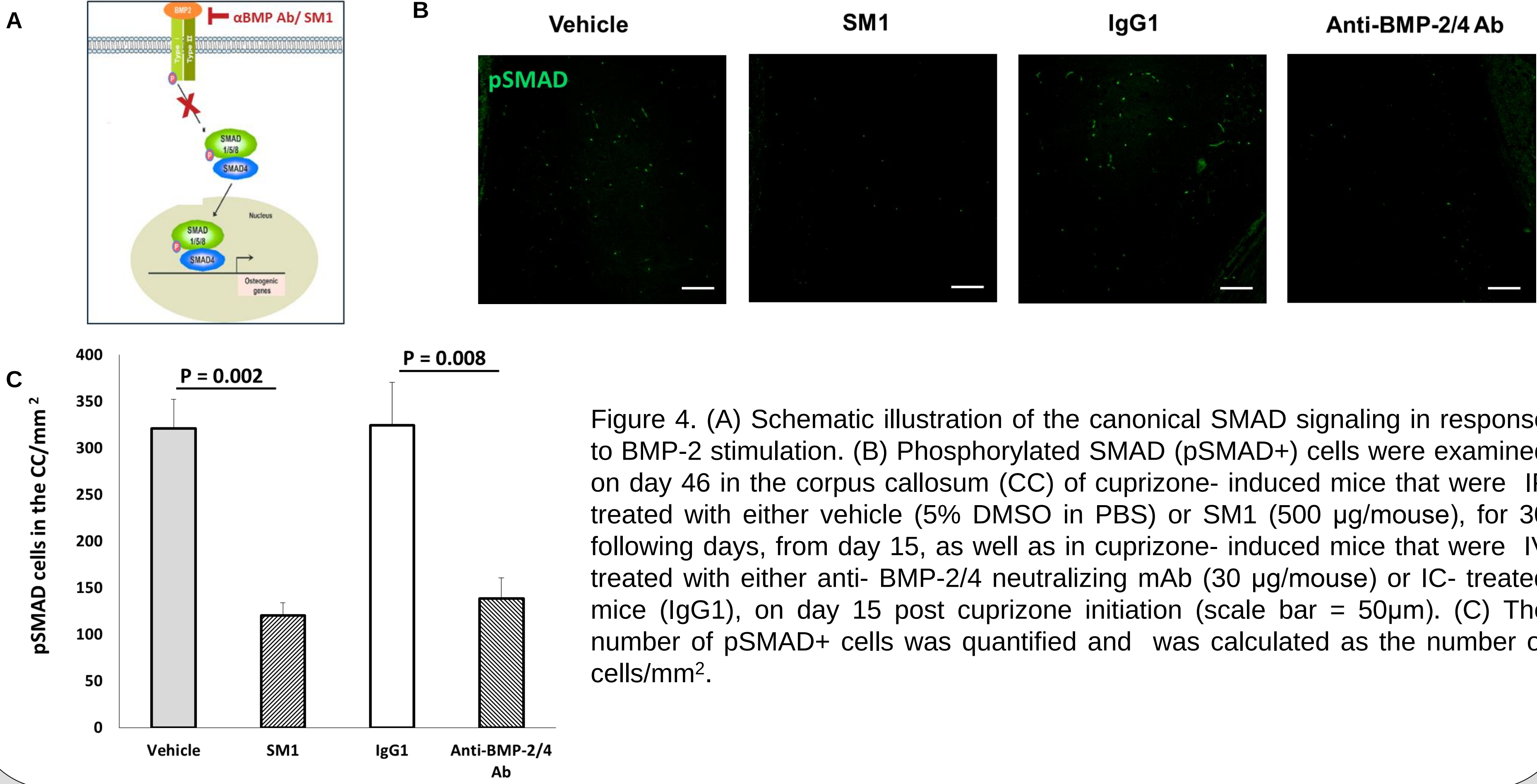
I. Anti- BMP-2/4 mAb and SM1 promote remyelination in the corpus callosum of cuprizone- induced mice



II. Anti- BMP-2/4 mAb and SM1 enhance OPCs differentiation into mature Olig-2⁺CC1⁺ oligodendrocytes in the corpus callosum of cuprizone- induced mice



III. Anti- BMP-2/4 mAb and SM1 reduce SMAD phosphorylation in the corpus callosum of cuprizone- induced mice



CONCLUSIONS

- Systemic administration of either SM1 or anti- BMP-2/4 neutralizing Ab to cuprizone- induced mice induce enhanced myelination and oligodendrocytes maturation together with BMP2/4 signaling inhibition.
- Anti- BMP-2/4 Ab or SM1 are potential therapies for oligodendrocytes differentiation and remyelination in demyelinating disease such as multiple sclerosis.

DISCLOSURE

The study was supported by Stem Cell Medicine Ltd.