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Selective PDE4 subtype inhibition provides new opportunities to intervene in neuroinflammatory versus myelin damaging hallmarks of multiple sclerosis

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Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by focal inflammatory lesions and prominent demyelination. Even though the currently available therapies are effective in treating the initial stages of disease, they are unable to halt or reverse disease progression into the chronic progressive stage. Thus far, no repair-inducing treatments are available for progressive MS patients. Hence, there is an urgent need for the development of new therapeutic strategies either targeting the destructive immunological demyelination or boosting endogenous repair mechanisms. Using *in vitro*, *ex vivo,* and *in vivo* models, we demonstrate that selective inhibition of phosphodiesterase 4 (PDE4), a family of enzymes that hydrolyzes and inactivates cyclic adenosine monophosphate (cAMP), reduces inflammation and promotes myelin repair. More specifically, we segregated the myelination-promoting and anti-inflammatory effects into a PDE4D- and PDE4B-dependent process respectively. We show that inhibition of PDE4D boosts oligodendrocyte progenitor cells (OPC) differentiation and enhances (re)myelination of both murine OPCs and human iPSC-derived OPCs. In addition, PDE4D inhibition promotes *in vivo* remyelination in the cuprizone model, which is accompanied by improved spatial memory and reduced visual evoked potential latency times. We further identified that PDE4B-specific inhibition exerts anti-inflammatory effects since it lowers *in vitro* monocytic nitric oxide (NO) production and improves *in vivo* neurological scores during the early phase of experimental autoimmune encephalomyelitis (EAE). In contrast to the pan PDE4 inhibitor roflumilast, the therapeutic dose of both the PDE4B-specific inhibitor A33 and the PDE4D-specific inhibitor Gebr32a did not trigger emesis-like side effects in rodents. Finally, we report distinct *pde4d* isoform expression patterns in human area postrema neurons and human oligodendroglia lineage cells. Using the CRISPR-

Cas9 system, we confirmed that PDE4D1/2 and PDE4D6 are the key targets to induce OPC differentiation. Collectively, these data demonstrate that gene specific PDE4 inhibitors have potential as novel therapeutic agents for targeting the distinct disease processes of MS.