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Demyelination in Organotypic Slice Cultures is Attenuated by BAF312 (Siponimod)

O'Sullivan C*

Drug Development, School of Medicine, Trinity College, Dublin, Ireland

The therapeutic value of sphingosine-1 phosphate receptor (S1PR) modulation was highlighted by the success of fingolimod (pFTY720) in the clinical management of relapsing remitting multiple sclerosis (MS). Great effort was then made to generate high selectivity agonists towards certain S1PR subtypes. Of particular interest were agonists with selectivity towards the S1PR1 subtype with little or no activity at the S1PR3. This was in large part due to preclinical studies in mice that suggested the transitory bradycardia that occurred after the introductory dose of pFTY720 may be attributable to the S1PR3 subtype [1,2]. Furthermore, favourable properties associated with the S1PR1 and S1PR5 subtypes, such as the key role S1PR1 plays in lymphocyte migration and the reported role of S1PR5 on oligodendrocyte function and myelination, made these attractive receptor subtypes to target [3,4]. This resulted in the synthesis of BAF312 (Siponimod), a second generation S1PR modulator selective towards the S1PR1/S1PR5 subtypes [1].

To date, BAF312 has been investigated in a number of early phase clinical trials for the treatment of secondary progressive MS (NCT01665144), relapsing remitting MS (NCT00879658), Polymyositis (NCT01801917) and Dermatomyositis (NCT02029274). In a recent article from Prof. Kumlesh Dev's lab (Trinity College), the effect of BAF312 on isolated glia cultures and slice culture models of demyelination were investigated [5]. Treatment of mouse and human astrocytes with BAF312 modulated the levels of ERK and AKT phosphorylation and Ca2+ signalling pathways. Similar to pFTY720, BAF312 also induced S1PR1 internalization in astrocyte cultures [5]. Notably, a difference in the coupling of S1PR1 and S1PR3 to pAKT and pERK in mouse and human astrocytes was seen. S1PR1 appeared to play a more central role in pERK and pAKT signalling in mouse astrocytes while S1PR3 and S1PR1 had a comparable effect in regulating pERK and pAKT levels in human astrocytes [5]. The importance of a species dependent difference between S1PR1 and S1PR3 function in mice and humans has not yet been elucidated. However, in an age where preclinical studies of many if not most drugs are performed in rodents it is highly relevant to our drug discovery that such species dependent differences are considered.

Slice cultures are an established *in-vitro* assay for the study of myelin development and maintenance and represent an excellent compromise between single cell cultures and *in-vivo* animal studies. Unlike single cell cultures, organotypic slice cultures preserve the architecture of the brain regions that they originate from and can more accurately represent the complex processes and interactions that occur between cells and their microenvironment. Such slice cultures have been an invaluable tool in the study of CNS S1PRs and their roles in myelination. Treatment of slices with lysophosphatidylcholine (LPC), a demyelinating agent, has been used as a model to investigate the effects of S1PRs on demyelination [6,7]. Treatment of organotypic slice cultures with BAF312 reduced the levels of IL6 induced by LPC, and more importantly attenuated the demyelination induced by LPC. In addition, psychosine, (toxic lipid metabolite), which accumulates in the brains of patients with Krabbe disease (KD), also induced demyelination in these organotypic slice cultures [5]. Interestingly, this psychosine-induced demyelination was not associated with changes in the levels of IL6 and importantly, was also attenuated by BAF312. In summary, the O'Sullivan et al study reported that BAF312 can modulate a number of glial cell functions as well as attenuate psychosine and LPC-induced demyelination, highlighting this drug as a promising therapy for demyelinating diseases.

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***Corresponding author:** Catherine O'Sullivan, Drug Development, School of Medicine, Trinity College, Dublin, Ireland, E-mail: osullc12@tcd.ie.

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