

Technology Opportunity, Ref. No. UB-18/198

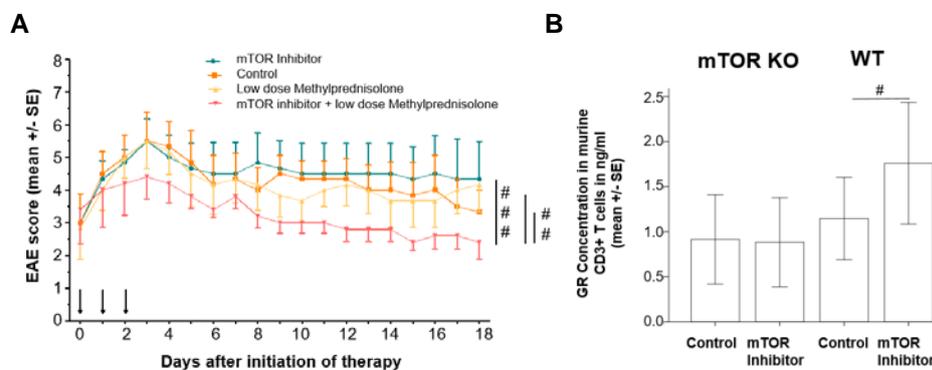
## mTOR Inhibitor-Glucocorticoid Combination Therapy For Treatment Of Multiple Sclerosis Relapses

Co-administration of any mTOR inhibitor increases the efficacy of a glucocorticoid (GC)-“pulse” therapy given on three consecutive days. This invention provides a unique opportunity for an enhanced treatment approach for multiple sclerosis (MS) relapses, which still occur frequently and for which no other first line treatment option exists apart from intravenous (iv) steroids.

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**Background** In contrast to an broad armamentarium of approved disease modifying therapies (DMT), high dose iv GC-“pulse” therapy is the only approved 1<sup>st</sup> line treatment option for acute MS relapses. Still, approximately 40% of patients do not improve sufficiently which is a major reason for disability accrual in relapsing MS patients. Thus, increasing the efficacy of GC treatment for MS relapses represents a major medical need.

**Invention** We have demonstrated that pharmacological inhibition of mTOR with a variety of different mTOR inhibitors leads to augmented glucocorticosteroid effects both *in vitro* (steroid-induced T-cell apoptosis) and in the animal model of MS. This synergistic effect of mTOR inhibition is mediated via an upregulation of the glucocorticoid receptor. Different mTOR inhibitors show similar experimental results: everolimus, rapamycin, temsirolimus, AZD 2014, palomid 529, omipalisib, voxtalisib, dactolisib, XL 388 and Torin I.



**(A)** Experimental Autoimmune Encephalomyelitis (EAE) treated with an mTOR inhibitor and low dose methylprednisolone over three consecutive days. Red curve represents dual treatment. n=6 animals each, Kruskal-Wallis Test: ##  $\leq 0.01$ , ###  $\leq 0.001$ . EAE Score: Score 2 represents a tail paresis, score 4 a gait ataxia and Score 6 a paraparesis. **(B)** GR concentration after incubation of murine CD3+ T cells (WT vs. mTOR KO) with an mTOR inhibitor *in vitro* (24h; n=5, ELISA). Wilcoxon signed-rank test: #  $< 0.05$ . Abbreviations: GR: Glucocorticoid Receptor; KO: Knock out; SE: Standard Error.

**Fields of Use** MS relapse treatment: Administration of an mTOR inhibitor in combination with intravenous glucocorticoids

**Patent Status** PCT patent application filed

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