**Rolipram Therapy Inhibits Important Immunoregulatory Circuits in Patients with Multiple Sclerosis**

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**Background**: Rolipram, a PDE-4 inhibitor, was shown to be effective for Th1-mediated autoimmune disease animal models and human in-vitro studies. M.S. is believed to be a Th1 mediated autoimmune disease, but when Rolipram was used in a phase I/II trial it actually increased inflammatory lesions in the brain. The purpose of this study was to explain the discrepancy between animal/in-vitro data and the human results.
**Hypothesis**: Our first hypothesis was that Rolipram by decreasing IL-2 production, and by modifying IL-2 signaling may have a deleterious effect on the $FoxP3^{+}$ $CD4^{+}$ T-regs and $CD56^{bright}$ NK cells, both important regulatory cells. Our second hypothesis was that Rolipram by decreasing IFN-gamma production which is inhibitory for IL-17 production by $CD4^{+}$ T-cells, would in turn result in an increase of deleterious IL-17 production with encephalitogenic potential.
**Methods**: 8 Cryopreserved PBMC with paired baseline and Rolipram therapy samples were thawed. The percentage of FoxP3+ T-regs, percentage of $CD56^{bright}$ NK cells, and proliferation of immune cell subpopulations in vitro using Ki-67 antigen were determined using 6 color flow cytometry. Further, T-cells were polyclonally activated by CD3/CD28 microbeads for 7 days, and their cytokine production was determined by intracellular staining.
**Results**:We were able to demonstrate a statistically significant decrease in $FoxP3^{+}$ T-regs, and a trend towards a decrease in $CD56^{bright}$ NK cells and their in-vivo proliferation during Rolipram therapy. In contrast to our second hypothesis we observed a statistically significant decrease in production of IL-17 cytokines, even though we saw a decrease in IFN-gamma production by $CD4^{+}$ T-cells.
**Conclusion:**We demonstrated Rolipram therapy inhibits important immunoregulatory circuits, which may explain the increase in the inflammatory activity observed in MS patients. Yet our data also poses questions about the importance of Th1 and Th17 cells in the MS disease process.