**Project #23. Title: Use of Dimethyl Fumarate in Type 1 Diabetes**

**Award Period: 06/01/20** - **05/31/21 Final Report**

**PI: Drs Francesco Vendrame and Allison Bayer**

Type 1 diabetes (T1D) in an autoimmune disease where the body's own immune system mistakenly destroys the insulin-producing cells in the pancreas [1]. Therapies targeting this immune response have demonstrated some efficacy, but these outcomes are not generally sustained [2]. New strategies able to create more lasting effects are therefore needed. To this end we proposed to investigate whether dimethyl fumarate (DMF) can be used as a novel therapeutic agent for T1D. DMF is an FDA approved medication for the treatment of another autoimmune disease called relapsing remitting multiple sclerosis [3]. Data in the animal model of multiple sclerosis and humans have shown that DMF significantly improves clinical outcomes by targeting the immune response through mechanisms which supports the rationale of testing DMF in T1D [4]. Thus, the aim of this proposal is to conduct preclinical investigations in the NOD mouse model, a widely accepted model of T1D, to test whether DMF can antagonize autoimmunity in the early stages of the disease.

![Chart

Description automatically generated with low confidence]()Our results show that 12-weeks DMF treatment starting in 10-weeks-old NOD mice prevents diabetes onset and that this associated with a preservation of glucose tolerance (Fig 1A, B). Importantly the protective effect of DMF on diabetes prevention is long lasting and persists despite stopping treatment (Fig 1A). Investigations aimed at the understanding the mechanisms involved in DMF protection show that DMF inhibits the secretion of pro-inflammatory cytokines in immune cell subset such as CD4, CD8 and NK cells. In particular, in treated mice DMF is able to modulate autoimmunity by reducing the production of the pro-inflammatory cytokine IFN- γ compared to mice that did not receive DMF (Fig 1C).

We are now completing our studies by characterizing the pathology of the pancreatic islets from mice treated with DMF compared to mice which did not receive treatment. Overall, these results support a protective role for DMF in T1D. Importantly, based on our findings we have a created a working group with other investigators with the goal of launching a clinical trial and test the effect of DMF in patients with newly diagnosed T1D.

Bibliography

1. Katsarou, A., Gudbjornsdottir, S., Rawshani, A., Dabelea, D., Bonifacio, E., Anderson, B.J., Jacobsen, L.M., Schatz, D.A., Lernmark, A.: Type 1 diabetes mellitus. Nature reviews. Disease primers **3**, 17016 (2017). doi:10.1038/nrdp.2017.16

2. Greenbaum, C., VanBuecken, D., Lord, S.: Disease-Modifying Therapies in Type 1 Diabetes: A Look into the Future of Diabetes Practice. Drugs **79**(1), 43-61 (2019). doi:10.1007/s40265-018-1035-y

3. Montes Diaz, G., Hupperts, R., Fraussen, J., Somers, V.: Dimethyl fumarate treatment in multiple sclerosis: Recent advances in clinical and immunological studies. Autoimmunity reviews **17**(12), 1240-1250 (2018). doi:10.1016/j.autrev.2018.07.001

4. Mills, E.A., Ogrodnik, M.A., Plave, A., Mao-Draayer, Y.: Emerging Understanding of the Mechanism of Action for Dimethyl Fumarate in the Treatment of Multiple Sclerosis. Frontiers in Neurology **9**, 5 (2018). doi:10.3389/fneur.2018.00005