**Characterization Studies of the Multiple Autoimmune Disease (MAD) Rat: Type 1 Diabetes**

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**INTRODUCTION**

Biomedical Research Models, Inc. has developed an inbred rat strain susceptible to multiple autoimmune diseases (MAD). The MAD rats were derived from congenic LEW1-WI rats. During inbreeding (F0) selection was made for autoimmune features. The goal was to develop a reliable model to test the efficacy of treatments designed to prevent or reverse autoimmune diseases and for screening for adverse effects of these therapies.

**METHODS**

A panel of TLR agonists was tested for their ability to induce T1D in MAD rats. We hypothesized that appropriate activation of immune cells that initiate T1D in genetically susceptible hosts may lead directly to overt disease. The doses were chosen based on previous studies that demonstrated diabetogenicity of certain TLR agonists in concert with Kilmarnock rat virus (KRV) infection in the MHC-related rat diabetes resistant R36A rat strain (67.5). Standard commercially available TLR agonists were administered at 0.1, 1, and 10 times the previously known to synergize with virus infections in BHR/Wor rats, but that are not diabetogenic in the absence of virus. We also tested both high and low molecular weight forms of poly I:C TLR agonists. Rats were dosed 3 days weekly by IP injection beginning at 21-24 days of age. Compounds were administered in 5-6 mg/kg TLR agonist for at least 1 week, or until a disease endpoint was achieved. Rats were treated over a 30 day period and were monitored for diabetes from 7 to 40 days after the initiation of treatment. In addition to screening for T1D, rats treated with TLR ligands were also examined for evidence of inflammatory arthritis, the presence of which would be an off-target effect of the induction procedure. Diabetes can be induced in the class II MHC-identical BBDR/Wor rat strain only up to 24-28 days of age, after which they show resistance to induction (unpublished data). We proposed to investigate the window of age susceptibility in the MAD rat strain to further characterize the model and potentially enhance future application of regimens aimed at prevention/reversal of diabetes.

**RESULTS AND DISCUSSION**

- **Administration of our historical standard poly IC (primarily HMW) dose of 1.0 mg/kg resulted in a high incidence of T1D in MAD rats in rats of both genders (Table 1).**

  - **The NW composition of the poly IC material has no apparent effect on T1D onset in this model (Table 2).** It has been reported that HMW poly IC signals through pathways different from those activated by the low molecular weight (LMW) form, with potential implications in autoimmune disease (45). Since both HMW and LMW preparations induced comparable frequencies of T1D at similar doses and with similar kinetics in both genders, this data suggests that a broad spectrum of double stranded RNA molecular species may be able to trigger autoimmune diabetes in susceptible hosts (HMW through MD2A signaling pathway and LMW through MD2 signaling pathway).

- **Zymosan (Table 3) and R848 (Table 4) showed a substantial ability to induce diabetes in this rat strain, whereas Cpg (Table 5) failed to cause glycyruria or elevated blood glucose levels in MAD rats.** These TLR study results are presented in Table 6.

- **Diabetes can be induced in the class II MHC-identical BBDR/Wor rat strain only up to 24-28 days of age, after which they show resistance to induction (unpublished data).** We proposed to investigate the window of age susceptibility in the MAD rat strain to further characterize the model and potentially enhance future application of regimens aimed at prevention/reversal of diabetes. As shown in Table 6, induction of T1D with standard dose poly IC is highly efficient when treatment is started up to 34 days of age (66-75%) but disease penetrance then diminishes significantly at 41-44 days of age (27%) (Table 7). These findings will allow for a larger window for preclinical with potential T1D therapies for more flexible experimental designs in future studies.

**REFERENCES**


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