



## **ImmunoMolecular Therapeutics’ Scientific Co-founder Presents a Novel Small Molecule Approach to Blocking the Autoimmunity in Type 1 Diabetes**

*-- Approach presented at the American Diabetes Association 78th Scientific Sessions --*

*-- Methyldopa found to selectively bind to DQ8, and inhibit the autoimmune cascade. Strong signal for efficacy established in a Phase 1b clinical trial in patients with recent-onset type 1 diabetes --*

BROOMFIELD, Colo. – June 25, 2018 – ImmunoMolecular Therapeutics (IM Therapeutics), a company developing personalized small molecule therapies for the treatment of genetically defined autoimmune diseases, today announced the presentation of a novel approach to blocking the autoimmunity in type 1 diabetes (T1D) by IM Therapeutics Chief Scientific Officer and co-founder, Aaron Michels, M.D. at the American Diabetes Association 78<sup>th</sup> Scientific Sessions.

The presentation titled, “From Mechanism to Clinical Trial—Methyldopa for Type 1 Diabetes Prevention” explores how a research team led by Dr. Michels and IM Therapeutics Chief Medical Officer and co-founder Peter Gottlieb, M.D. of the Barbara Davis Center for Diabetes at the University of Colorado, Denver, successfully elucidated the mechanism of action and basic science behind the activity of methyldopa (MDOPA) as an innovative small molecule approach to block the autoimmune response in T1D. Dr. Michels also discusses results from a Phase 1b clinical trial in patients with recent-onset T1D, in which MDOPA showed a strong signal for efficacy. The results were published earlier this year in a paper titled, “Methyldopa blocks MHC class II binding to disease-specific antigens in autoimmune diabetes,” in the *Journal of Clinical Investigation* (<https://www.jci.org/articles/view/97739>).

In T1D, the immune system abnormally recognizes insulin as a foreign peptide, and over time mounts an attack that destroys insulin-producing beta-cells in the pancreas, effectively eliminating the body’s ability to produce this important hormone. The human leukocyte antigen (HLA)-DQ8 genetic variant is present in 50-60% of T1D patients and is the most significant genetic factor in predisposing an individual to acquire T1D. Its protein product, a major histocompatibility (MHC) class II molecule, is known to abnormally bind and present particular self-peptides to autoreactive T cells. Drs. Michels and Gottlieb and their collaborators hypothesized that blocking DQ8 antigen presentation with a small molecule could provide therapeutic benefit by preventing recognition of self-peptides by the immune system’s pathogenic T-cells.

“Once beta-cell function is lost, T1D patients will be forever dependent on an external source of insulin. A drug that prevents the pathologic immune activity like the one described in today’s presentation, could save beta-cell function early on, and help these patients avoid a lifetime of injections and the risks associated with diabetes,” said Dr. Michels. “In our study we show a new approach for treating autoimmune diseases, using MDOPA, which specifically blocked DQ8 in recent-onset patients with T1D, and reduced inflammatory T-cell responses toward insulin.”



In his presentation, Dr. Michels describes the discovery process that identified MDOPA as a selective binding pair for DQ8 and the subsequent pre-clinical validation of this binding mechanism's ability to block diabetes specific T cells, but not influenza T cells, activated by DQ8. A small molecule of similar structure delayed diabetes onset in the non-obese diabetic (NOD) mouse model of spontaneous autoimmune diabetes. A rational structure-based approach was used to evaluate the 'druggability' of pockets in the antigen-binding cleft of the T1D risk associated HLA-DQ8 molecule. MDOPA, currently approved by the FDA to treat hypertension, was predicted to bind this pocket, with binding validated *in vitro* and in an animal model. The preclinical findings were translated to human T1D in a single-arm open-label Phase 1b dose escalation study ([NCT01883804](#)), where MDOPA treatment was evaluated for safety and signals of efficacy to block DQ8. Study results showed that DQ8 presentation was inhibited compared to baseline levels, with 17/20 patients showing a response. Additionally a subset of patients had reduced inflammatory T-cell responses toward insulin. In addition, MDOPA was shown to be well-tolerated, with no serious adverse events.

"These results, in both the preclinical and the clinical research settings, further validate the importance of HLA molecules as drug targets for autoimmune diseases, and the ability of a small molecule inhibitor approach to potentially mitigate the progression of disease," said Dr. Gottlieb. "Our lead candidate in development, IMT-002, is a proprietary formulation of the D enantiomer of MDOPA and is being developed to maintain the benefits that MDOPA has in T1D, such as specific binding to the peptide binding groove of DQ8 to block pathogenic function, while avoiding side effects such as lowering blood pressure. We are extending the discovery process described in Dr. Michels' presentation to Celiac Disease by targeting HLA-DQ2, which is highly prevalent in Celiac patients."

The research team included collaborators from the University of Florida, University of Colorado, and Novartis Institutes for Biomedical Research.

### **About Type 1 Diabetes**

Type 1 diabetes (T1D) is a polygenetic disorder that affects the insulin producing beta-cells in the pancreas, categorized by a lack of sufficient insulin production, which prevents tissues from utilizing glucose, leading to high blood sugar. Insulin production is slowed when T and B cells react to self-antigens in the islets of the pancreas where the body's insulin-producing beta-cells reside. The human HLA-DQ8 gene is the most significant factor in predisposing an individual to acquire T1D. The DQ8 gene is present in 50-60% of T1D patients and its protein product (a major histocompatibility class II molecule) is known to abnormally bind and present particular autoantigen peptides to autoreactive T cells.

### **About IMT-002**

IMT-002 (D-methylidopa) is an oral small molecule drug being developed to treat T1D in patients with the HLA-DQ8 gene. IMT-002 occupies the peptide binding groove of DQ8 present on the surface of antigen presenting cells where diabetogenic peptides such as insulin are presented to CD4 T-lymphocytes to initiate the autoimmune cascade. When HLA-DQ8 function is inhibited, the immune system will no longer attack insulin producing beta-cells, thus creating the potential for at risk or early



stage patients to maintain normal insulin production. IMT-002 has been granted Orphan Drug status by the U.S. FDA.

**About IM Therapeutics**

IM Therapeutics is developing personalized immuno-therapeutic drugs for autoimmune diseases based on the genetic risk attributed by human leukocyte antigen genes. The lead candidate drug is an oral small molecule that starves the autoimmune process in type 1 diabetes by blocking DQ8 on specific immune cells. Our goal is to preserve pancreatic beta-cell function and maintain normal insulin production in at-risk and early-stage patients with type 1 diabetes.

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