

Use of biosimulation to identify novel strategies for inducing type 1 diabetes remission in the NOD mouse

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Type 1 diabetes (T1D) is a complex, multifactorial disease characterized by T cell-mediated autoimmune destruction of insulin-secreting pancreatic β cells. Because female non-obese diabetic (NOD) mice exhibit disease characteristics similar to human T1D, including spontaneous development of insulin-dependent diabetes, this animal model is widely used to investigate potential therapies. While numerous interventions have been shown to be effective in preventing diabetes onset in NOD mice, few treatment strategies have been shown to reverse established disease [1]. In this study, the Type 1 Diabetes PhysioLab[®] platform, a computer model of the NOD mouse, was used to identify potential interventions of biological pathways (e.g., modulation of specific cellular functions or soluble mediator effects) that can induce disease remission.

The Type 1 Diabetes PhysioLab[®] platform is a large-scale, ordinary differential equation (ODE)-based mechanistic model that describes the pathophysiology of pancreatic islet β cell autoimmunity and tolerance in a female NOD mouse from birth through diabetes onset [2]. The model encompasses key biological processes in the pancreatic lymph node (PLN) and pancreatic islets, as well as the trafficking of cells and proteins between the tissues. Specifically, the dynamic contribution of dendritic cells (DCs), macrophages, CD4+ and CD8+ T lymphocytes, B lymphocytes, regulatory T cells, natural killer (NK) cells, and pancreatic β cells to disease pathogenesis are represented. Emergent behaviors of the quantitative model (referred to as the “virtual” NOD mouse), including disease progression (e.g., diabetes onset time and cellular dynamics) and responses to multiple therapies are consistent with published data [2].

Biosimulations were conducted in the platform to evaluate the impact of individually modulating 275 different biological pathways on established diabetes. The quantitative strength of each pathway were reduced or enhanced by 100 fold continuously beginning after disease onset and their effects on disease were analyzed over a simulated 35 week period. Several metabolic pathways were found to induce remission when modulated individually, including increased glucose sensitivity to insulin, β cell replication and insulin synthesis, and reduced β cell exhaustion. However, continued modulation was required to prevent disease relapse. Remarkably, while no single immunologic pathway was sufficient to induce remission even when continuously modulated, specific combinations of immunological pathways or metabolic and immunological pathways were able to reverse disease with transient modulation. For example, increased innate regulatory T cell (iTreg) proliferation, combined with either increased β cell replication or decreased CD8+ activation, induced stable remission following an modulation period as short as two weeks (Figure 1). These results suggest that simultaneously targeting multiple immunologic pathways or together with pathways affecting islet β cell

turnover, may be an effective strategy to induce long-term remission of diabetic NOD mouse. Findings of this study can provide novel insights to the design of effective treatments for T1D patients.

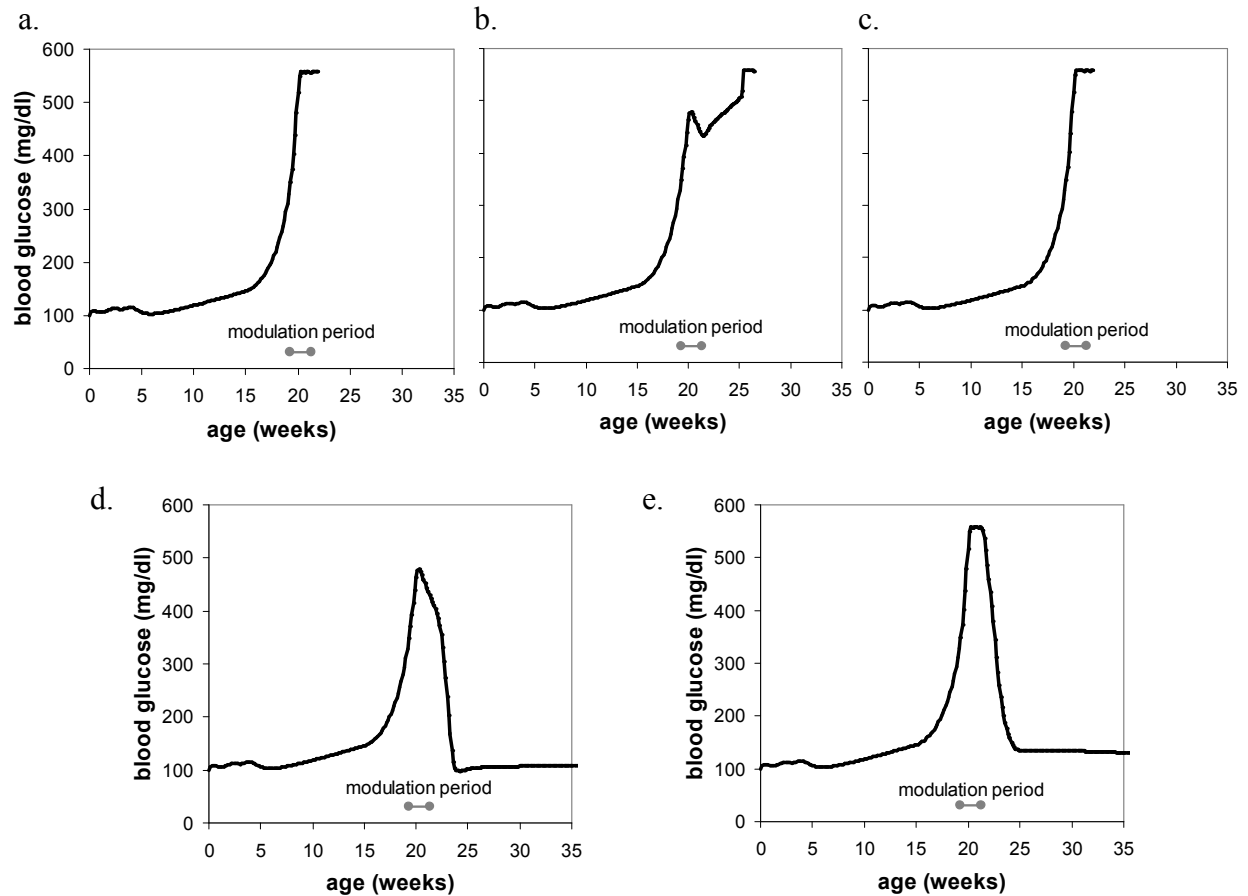


Figure 1. Simulated effects of modulating iTreg, β cell and CD8+ T cell pathways individually and in combination after diabetes onset. In these simulations, pathway modulations were conducted for 2 weeks, beginning after diabetes onset (defined as the age of the virtual NOD mouse at which blood glucose first rises above 350mg/dl). a, increased iTreg proliferation (5x); b, increased β cell replication (6x); c, reduced CD8+ T cell activation (50%); d, increased iTreg proliferation (5x) and β cell replication (6x); e, increased iTreg proliferation (5x) and reduced CD8+ T cell activation (50%).

References

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