

CLAIMS

What is claimed is:

1. A method of preventing or delaying the onset of clinical type 1 diabetes (T1D), comprising:
 - providing a non-diabetic subject who is at risk for T1D;
 - administering a prophylactically effective amount of an anti-CD3 antibody to the non-diabetic subject; and
 - determining, prior to or after the administering step, that the non-diabetic subject has more than about 5% to more than about 10% TIGIT+KLRG1+CD8+ T-cells in all CD3+ T cells, which is indicative of successful prevention or delay of the onset of clinical T1D.
2. The method of claim 1, wherein the non-diabetic subject is a relative of a patient with T1D.
3. The method of claim 1, further comprising determining that the non-diabetic subject (1) is substantially free of antibodies against zinc transporter 8 (ZnT8), (2) is HLA-DR4+, and/or (3) is not HLA-DR3+.
4. The method of claim 3, wherein the non-diabetic subject has 2 or more diabetes-related autoantibodies selected from islet cell antibodies (ICA), insulin autoantibodies (IAA), and antibodies to glutamic acid decarboxylase (GAD), tyrosine phosphatase (IA-2/ICA512) or ZnT8.
5. The method of claim 1, wherein the non-diabetic subject has abnormal glucose tolerance on oral glucose tolerance test (OGTT).
6. The method of claim 5, wherein the abnormal glucose tolerance on OGTT is a fasting glucose level of 110-125 mg/dL, or 2 hour plasma of ≥ 140 and < 200 mg/dL, or an intervening glucose value at 30, 60, or 90 minutes on OGTT > 200 mg/dL.
7. The method of claim 3, wherein the non-diabetic subject does not have antibodies against ZnT8.
8. The method of claim 3, wherein the non-diabetic subject is HLA-DR4+ and is not HLA-DR3+.
9. The method of claim 1, wherein the anti-CD3 antibody is selected from teplizumab, oteelixizumab or foralumab.
10. The method of claim 9, wherein the prophylactically effective amount comprises a 10 to 14 day course of subcutaneous (SC) injection or intravenous (IV) infusion or oral

administration of the anti-CD3 antibody at 10-1000 micrograms/meter squared ($\mu\text{g}/\text{m}^2$), preferably a 14-day course IV infusion at 51 $\mu\text{g}/\text{m}^2$, 103 $\mu\text{g}/\text{m}^2$, 207 $\mu\text{g}/\text{m}^2$, and 413 $\mu\text{g}/\text{m}^2$, on days 0–3, respectively, and one dose of 826 $\mu\text{g}/\text{m}^2$ on each of days 4–13.

11. The method of claim 9, wherein the prophylactically effective amount delays median time to clinical diagnosis of T1D by at least 50%, at least 80%, or at least 90%, or at least 12 months, at least 18 months, at least 24 months, at least 36 months, at least 48 months, or at least 60 months.
12. The method of any one of claims 1-11, wherein said determining of TIGIT+KLRG1+CD8+ T-cells is by flow cytometry.
13. The method of any one of claims 1-11, further comprising determining a decrease in a percentage of CD8+ T cells expressing proliferation markers Ki67 and/or CD57.
14. A method of prognosing responsiveness of an anti-CD3 antibody in preventing or delaying the onset of type 1 diabetes (T1D), comprising:
 - providing a non-diabetic subject who is at risk for T1D;
 - administering a prophylactically effective amount of an anti-CD3 antibody to the non-diabetic subject; and
 - determining C-peptide area under the curve (AUC): glucose AUC ratio, wherein an increase in said ratio indicates responsiveness to the anti-CD3 antibody and/or non-progression to clinical T1D.