

risk for development of clinical disease with overt hyperglycemia and requirement for insulin treatment (Stage 3). Several immune interventions have been shown to delay decline in beta cell function when studied in recent-onset clinical T1D. One promising therapy is the FcR non-binding anti-CD3 monoclonal antibody teplizumab, as several studies have shown that short-term treatment reduces loss of β cell function durably, with an observable effect seen as long as 7 years after diagnosis and treatment. The drug modifies the function of CD8⁺ T lymphocytes, which are thought to be important effector cells that cause beta cell killing.

[0006] To date, no intervention initiated before the clinical diagnosis (i.e., at Stage 1 or 2) has altered progression to clinical, Stage 3 T1D. Thus, a need exists for a treatment that would prevent or delay the onset of clinical T1D in high-risk individuals.

SUMMARY

[0007] 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.

[0008] In some examples, the non-diabetic subject is a relative of a patient with T1D.

[0009] In some examples, the method further includes 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⁺.

[0010] In some examples, 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.

[0011] In some examples, the non-diabetic subject has abnormal glucose tolerance on oral glucose tolerance test (OGTT). In some examples, 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.

[0012] In some examples, the non-diabetic subject does not have antibodies against ZnT8.

[0013] In some examples, the non-diabetic subject is HLA-DR4+ and is not HLA-DR3+.

[0014] In some examples, the anti-CD3 antibody is selected from teplizumab, oteelixizumab or foralumab. In some examples, the prophylactically effective amount of the antibody 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.

[0015] In some examples, 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.

[0016] In some examples, the determining of TIGIT+KLRG1+CD8+ T-cells is by flow cytometry.

[0017] In some examples, the method further includes determining a decrease in a percentage of CD8+ T cells expressing proliferation markers Ki67 and/or CD57.

[0018] 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.

[0018a] In one aspect, the present disclosure relates to use of a prophylactically effective amount of an anti-CD3 antibody in the manufacture of a medicament for preventing or delaying the onset of clinical type 1 diabetes (T1D), wherein the use comprises that the medicament is to be administered to a non-diabetic subject who is at risk for T1D; and determining, prior to or after administration, that the non-diabetic subject has more than 5% to more than 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1A shows a consort diagram of at-risk individuals enrolled into the teplizumab prevention study.

[0020] FIG. 1B shows that teplizumab treatment is associated with a sustained effect on Type 1 Diabetes progression over 923 days of follow-up. Updated Kaplan-Meier Curve based on 923

CLAIMS

What is claimed is:

1. Use of a prophylactically effective amount of an anti-CD3 antibody in the manufacture of a medicament for preventing or delaying the onset of clinical type 1 diabetes (T1D), wherein the use comprises
that the medicament is to be administered to a non-diabetic subject who is at risk for T1D; and
determining, prior to or after administration, that the non-diabetic subject has more than 5% to more than 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 use of claim 1, wherein the non-diabetic subject is a relative of a patient with T1D.
3. The use 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 use 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 use of claim 1, wherein the non-diabetic subject has abnormal glucose tolerance on oral glucose tolerance test (OGTT).
6. The use 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 use of claim 3, wherein the non-diabetic subject does not have antibodies against ZnT8.
8. The use of claim 3, wherein the non-diabetic subject is HLA-DR4+ and is not HLA-DR3+.
9. The use of claim 1, wherein the anti-CD3 antibody is selected from teplizumab, otelixizumab or foralumab.
10. The use 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 use 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 use of any one of claims 1-11, wherein said determining of TIGIT+KLRG1+CD8+ T-cells is by flow cytometry.
13. The use 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.